PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Griffiths *et al.*	Examiner:	Jehanne Souaya Sitton
Serial No.:	10/571,879	Group Art Unit:	1634
Filed:	January 29, 2007	Docket No.:	FISHR24.001APC

Confirmation No.: 2661

Title: HORMONE RECEPTOR GENES AND MIGRAINE SUSCEPTIBILITY

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF LYNETTE ROBYN GRIFFITHS UNDER 37 CFR §1.132

1. I, LYNETTE ROBYN GRIFFITHS of, 14 Ewart Street, Burleigh Heads, Queensland, 4220, Australia, am a co-inventor with respect to the abovementioned United States patent application. I am currently Director, Genomics Research Centre and the Griffith Health Institute, Griffith University, Gold Coast, Queensland, Australia and I attach herewith a copy of my *Curriculum Vitae* as **Exhibit A**.

2. I am aware of the Examiner's reasons for rejecting claims 1, 3-9, 11, 13, 14, 16-18, 20, 24, and 25 under 35 USC §112, first paragraph, for alleged lack of enablement in the Office Action mailed December 9, 2010. In raising this rejection, the Examiner has stated that "**applicants own replication study failed to provide statistically significant correlations**. Further, a number of studies have been undertaken to confirm the findings taught in the specification with little success. With regard to the ESR1 G2014A (rs2228480) polymorphism: Corominas (Corominas et al; European Journal of Neurology, vol 16, 413-415; 2009);

Kaunisto (Kaunisto et al; Cephalagia; vol 26, pages 1462-1472, 2006), and Oterino (Oterino et al; Neuroreport, vol 17, pages 61-64, 2006) teach that **no association was found for the ESR1 rs2228480 polymorphism**" (see, Office Action mailed December 9, 2010 at page 6; emphasis added).

3. As stated in the present application, the ESR1 G2014A (rs2228480) polymorphism was found to be positively associated with migraine in two independent case-control populations: population 1 genotypic P=0.008 and allelic P=0.003, population 2 genotypic $P=4x10^{-5}$ and allelic $P=8x10^{-6}$ (see, page 20, lines 10-26). The Examiner's insistence that there is no statistically significant correlation between these two populations ignores these genotype frequencies, and instead appears to focus on the fact that an association did not occur in males nor in the migraine without aura (MO) subgroup in the second population (see, page 20, lines 29-32 of the present application). This lack of association in these subgroups does not indicate that a statistically significant correlation between the two independent case-control populations does not exist. Rather, the lack of association in these subgroups reflects the small numbers of males (n=36) and MO sufferers (n=39) in the second population. Accordingly, sufficient power to make an association with these subgroups did not exist. However, when viewing the two independent case-control populations **overall**, the ESR1 G2014A (rs2228480) polymorphism was found to be positively associated with migraine, as seen in genotype frequencies of P=0.008 and $P=4x10^{-5}$, respectively and also the allele frequencies of P=0.003 and $P=8x10^{-6}$, respectively.

4. Similarly, a separate study of the PGR PROGINS polymorphism in the same two independent case-control populations also showed association with migraine "in the **total** group analysis": population 1 genotypic P=0.04, allelic P=0.017, population 2 genotypic P=0.019 and allelic P=0.003 (see, page 21, line 25 to page 22, line 7 of the present application; emphasis

added). Furthermore, analysis of both hormonal genes together showed that the interaction of the PGR PROGINS polymorphism combined with the ESR1 G2014A (rs2228480) polymorphism increased migraine risk by 3.2 (see, page 25, lines 13-16 of the present application).

5. The results of a systematic review and **meta-analysis** on the association between sex hormone receptor polymorphisms and migraine by Schürks *et al.* (*Cephalalgia* 30:1306-28, 2010), presented herewith as **Exhibit B**, independently support the conclusion that the estrogen receptor 1 gene (ESR1) G2014A (rs2228480) polymorphism is associated with migraine.

6. As stated on page 1312 of Schürks *et al.*, "[t]he pooled effect estimates among **all studies** suggest that the A allele is associated with an increased risk for any migraine (additive mode: pooled OR 1.37; 95% CI 1.02-1.83; Table 4)."

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6th June 2011

Lynette Robyn Griffiths

EXHIBIT A

CURRICULUM VITÆ
Lyn Robyn Griffiths

PERSONAL DETAILS

Name:	Lyn Robyn Griffiths	**Work Address:**	Genomics Research Centre Griffith Health Institute Griffith University PMB 50 GCMC Parklands Drive Southport QLD 4125
Nationality:	Australian		
Marital Status:	Married, 2 children		
Email:	l.griffiths@griffith.edu.au		
Tel no's:	Home +61 7 5535 0138 Work +61 7 5552 8664 Mobile+61(0)417 702 256	**Home Address:**	14 Ewart St Burleigh Heads QLD 4220
Fax no:	Work +61 7 5552 9081		

HIGHER EDUCATION/QUALIFICATIONS

Qualification	Institution	Year
High School Certificate	Fort Street Girls High, Sydney Dux (English, History, Science) School Captain	1969-1974
BSc (Hons.) Biochemistry	University of New South Wales	1980
PhD Medicine	University of Sydney	1990

CURRENT POSITIONS

Position	Institution
Professor	Molecular Genetics, Griffith University
Director	Griffith Health Institute
Dean	Research (Health), Griffith University
Director	Genomics Research Centre, Griffith University
Chair	Griffith Health Research Committee
President	Human Genetics Society of Australasia, QLD branch
Council Member	Queensland Institute Medical Research (QIMR)
Member	Scientific Program Committee for 2011 International Congress of Human Genetics (ICHG)
Chair	Local Organising Committee (LOC) for the 2011 HGSA Annual Scientific Meeting, Queensland
Member	NHMRC Postdoctoral Fellowships Panel
Deputy Chair	ARC Futures Fellowship Panel
Chair	Fulbright Commission Awards Panel (QLD)

AWARDS AND DISTINCTIONS

1984 -1987 NHMRC Biomedical Postgraduate Scholarship

1985	NSW Dept of Health Postgraduate Scholarship.
1986	Award Best Presentation, Human Genetics Society of Australia.
1987	Invited speaker 2nd Intl Conference on CMT Disorders, New York.
1987	Sponsored presenter, 9th Intl Human Gene Mapping Conference, Paris.
1996	Organised Human Genome Disorders symposium at Aust Society Medical Research.
1995-1998	Awards for a number of PhD Students at National and International conferences eg (S Rutherford; J Cook; L Haupt; S Selvey, the last two at a Gordon Cancer Conference in Rhode Island in 1998).
1995-present	Invited speaker at various conferences including recent Linkage Analysis Boden Conference, Neurogenetics Society and Australian Assoc of Neurologists meetings, Biotechnology Development Meeting, Norway and Intl Society Hypertension Satellite meeting in Amsterdam. Member of ASMR, High Blood Pressure Research Council, ASBMB, Human Genetics Society of Australia and American Human Genetics Society. Reviewer for NHMRC, ARC, QCF, NHF, Neurology and Human Genetics.
2000	Award, Best presentation International Headache Congress, Barcelona
2001	Most downloaded article for 2001Year in Molecular Cellular Probes
2001	Convenor, 40th ASMR National Scientific Conference, Gold Coast, November 2001 Convenor, 2nd Australasian Gene Mapping Meeting, Cairns QLD, July 2001
1999-2001	Director of Australian Society for Medical Research.
2003-2006	Chair, Scientific Program Committee, Intl Congress Human Genetics, Brisbane, 2006
2002-present	Member, Qld Institute Medical Research Council
2005-present	Chair, Griffith Health Research Committee
2003	Griffith University Commendation for Excellence in Teaching
2004	Centenary Medal Award for Distinguished Service to Education and Medical Research
2004	Gold Coast Honours Award (Education and Medical Research Category)
2005	Australian of the Year, Queensland Finalist
2006	Suncorp Queenslander of the Year Nominee
2006	Member of Board of Directors of CNN Future Summit
2006	Smart State – Smart Women Finalist (Research Scientist Category)
2009	Honorary Member for Golden Key Griffith University Chapter
2010	Research Excellence Award for Senior Researcher Griffith University

CAREER HISTORY

1975-1978	BSc, Double Major in biochemistry and microbiology	UNSW
1979	Honours Student and Tutor BSc(Hons) Thesis: "Leigh's Disease: Biochemical Studies"	Department of Biochemistry, UNSW
1980-1983	Research Assistant	Department of Medicine, University of Sydney.
1983-1984	Research Assistant	Department of Medicine, Duke University, NC, USA.
1984-1987	NH&MRC Biomedical Postgraduate Scholar (enrolled for PhD)	Department of Medicine, University of Sydney
1988	NSW Dept of Health Postgraduate Scholar and Tutor (part-time) PhD Thesis submitted- Title: "Chromosome 1 Gene Mapping with reference to Charcot-Marie-Tooth Disease". (PhD conferred March, 1990.)	Department of Medicine, University of Sydney
1989-1991	Chief Investigator and Sen Research Assist, NH&MRC Project Grant: "Molecular Genetic Abnormalities in Human Hypertension".	Department of Physiology, The University of Sydney.
1990	Lecturer in Genetics and Associate Director Biology 1	School of Biological Sciences, University of Sydney
1991	Lecturer in Genetics and Biochemistry	School of Biological Sciences, University of Sydney
1992-1994	Lecturer in Molecular Genetics, Cell Biology and Biochemistry	Applied Science, Griffith University
1995-1998	Senior Lecturer in Molecular Genetics and Cell Biology	School of Health Science, Griffith University
1998-2001	Associate Professor in Molecular Genetics and Cell Biology	School of Health Science, Griffith University
1997-present	Director, Genomics Research Centre	School of Health Science, Griffith University
2002-present	Professor in Molecular Genetics	School of Health Science, Griffith University
2004-2007	Head of School	School of Medical Science, Griffith University
2005-present	Chair, Griffith Health Research Committee	Griffith Health, Griffith Uni
2007-present	Dean, Research (Faculty of Health)	Griffith Health, Griffith Uni
2007-present	Director, Griffith Health Institute	Griffith University

RESEARCH EXPERIENCE

1979	*BSc Hons project, Department of Biochemistry, U.N.S.W.* Development of a radiochemical test to determine pyruvate dehydrogenase levels in patients with Leigh's Disease.
1980-1983	*Department of Medicine, University of Sydney.* The use of radioimmunoassay and bioluminescent tests to measure creatine kinase levels in Duchenne Muscular Dystrophy patients. Characterization of mouse platelet creatine kinase isoenzymes using electrophoresis. Stability studies of various enzymes and antibodies in the dried and liquid state. Development of a radioimmunoassay to diagnose patients with myasthenia gravis.
1983 - 1984	*Department of Medicine, Duke University, NC, U.S.A.* Preparation of a human liver cDNA library. Blood collection and preparation of DNA for myotonic dystrophy linkage studies. Genomic library screening and probe preparation.
1984 - 1988	*PhD project, Department of Medicine, University of Sydney.* Isolation, localization and identification of RFLP probes from a chromosome 1 library. Preparation of lymphoblast cell lines from patients with neurogenetic disorders. Genomic blotting and linkage studies on families with Charcot- Marie-Tooth disease using chromosome 1 RFLP probes. Linkage analysis using the LIPED computer programme and heterogeneity testing using the HOMOG programme.
1989 - 1991	*Department of Physiology, University of Sydney.* Development of probes and RFLPs for molecular genetic studies on human hypertension. Blood collection and preparation of DNA from normotensives, hypertensives and families with multiple affected members. Association and linkage studies using candidate gene probes and data computer analysis.
1992-Present	*Medical and Applied Science, Griffith University Gold Coast.* Molecular genetic studies on the basis of common human disorders including migraine and CVD genetic risk factors. Blood has been collected and DNA has been prepared from individuals, families with multiple affected members and also from isolated founder effect communities including Norfolk Island. DNA association and linkage studies, using microsatellite and SNP markers and candidate gene probes, are being performed on these populations. In addition gene studies on lymphoma, breast cancer and non-melanoma skin cancer and gene expression studies of multiple sclerosis are being undertaken. Development of NATA accredited DNA testing laboratory for neurogenetic disorders, as well as clinical trial studies

TEACHING EXPERIENCE

1979	Biochemistry II, Tutor and Demonstrator, Univ. of NSW.
1988	Biology I, Tutor and Demonstrator, Univ. of Sydney.
1989	Biology I, Tutor and Demonstrator, Cumberland College of Health Sciences.
1990	Admin Responsibilities as Associate Director of Biology I (1800 students) and Lecturer, Genetics and Biochemistry for Medicine, Dentistry and Science, School of Biological Sciences, Univ. of Sydney.
1991	Lecturer, Genetics and Biochemistry for Medicine, Dentistry and Science, School of Biological Sciences, Univ. of Sydney.
1992 - 1998	Lecturer, then Senior Lecturer in Molecular Genetics, Cell Biology and Biochemistry. Health and Applied Science, Griffith University
1998 - 2001	Associate Professor in Molecular Genetics and Cell Biology. Health Science, Griffith University.
2002 – present	Professor in Molecular Genetics. Medical Science, Griffith University.

POSTGRADUATE SUPERVISION - (27 completed, 14 current primary supervision RHD)

Primary Supervision

1990	Ying, L-H.	MSc(Qual.)	Dept. of Physiology, University of Sydney
1990-1993	Zee, R.Y.L.	PhD	Dept. of Physiology, University of Sydney
1995-1999	Nyholt, D.	PhD	Health Science, Griffith University
1996-2000	Cook, J.	PhD	Health Science, Griffith University
1995-2001	Haupt, L.	PhD	Applied Science, Griffith University
1995-2002	Rutherford, S.	PhD	Health Science, Griffith University
1995-2002	Selvey, S.	PhD	Applied Science, Griffith University
1997-2003	Rogers, K.	PhD	Health Science, Griffith University
1998-2003	Curran, J.	PhD	Health Science, Griffith University
1996-2003	Ashton, K.	PhD	Health Science, Griffith University
1997-2003	Lea, R.A.	PhD	Health Science, Griffith University
2001-2003	Sundholm, J.	MPhil	Health Science, Griffith University
1999-2004	Mellick, A.	PhD	Health Science, Griffith University
2000-2004	Carless, M.	PhD	Health Science, Griffith University
1999-2004	Tajouri, L.	PhD	Health Science, Griffith University
2000-2005	Johnson, M.P.	PhD	Health Science, Griffith University
2001-2005	Simcock, W.	PhD	Health Science, Griffith University
2003-2006	Curtain, R.	PhD	Health Science, Griffith University
2002-2005	Smith, R.A.	PhD	Health Science, Griffith University
2003-2007	Colson, N.J.	PhD	Health Science, Griffith University
2001-2008	Bellis, C.	PhD	Health Science, Griffith University
2002-2008	Culver, H.	PhD	Medical Science, Griffith University
2005-2009	Szvetko, A.L.	PhD	Medical Science, Griffith University
2005-2010	Hiesh, K.	PhD	Medical Science, Griffith University
2006-2009	Green, M.	PhD	Medical Science, Griffith University
2006-2008	Chickhani, S.	MPhil	Medical Science, Griffith University
2006-2010	Stephens, S	PhD	Medical Science, Griffith University
2007-present	Gabrovska, P.	PhD	Medical Science, Griffith University
2007 present	Cox.H	PhD	Medical Science, Griffith University
2007-present	Matovinovic, E.	PhD	Medical Science, Griffith University
2008-present	Fowder, J.	PhD	Medical Science, Griffith University
2008-present	Greely, R.	PhD	Medical Science, Griffith University
2008-present	Maher, B.	PhD	Medical Science, Griffith University
2008-present	Genesan,S.	PhD	Medical Science, Griffith University
2009-present	Camilleri, E.	PhD	Medical Science, Griffith University

2009-present	Aya Bonilla, C.	PhD	Medical Science, Griffith University
2009-present	McKenzie, J	PhD	Medical Science, Griffith University
2010-present	Benton, M	PhD	Medical Science, Griffith University
2010-present	McCartan, C	PhD	Medical Science, Griffith University
2010-present	Okpokam, N.	MPhil	Medical Science, Griffith University

Associate Supervision

1998-2001	Alfredson, D.	PhD	Health Science, Griffith University
1999-2001	Vaughan, T.	PhD	Health Science, Griffith University
2002-2006	Doecke, J.	PhD	Medical Science, Griffith University
2003-2006	Vanderlelie, J.	PhD	Medical Science, Griffith University
2003-2007	Stephens, A.	PhD	Medical Science, Griffith University
2004-2008	Shah, J.	PhD	Medical Science, Griffith University
2009-present	Cao, F.	PhD	MED/Med Science, Griffith University

POSTGRADUATE RESEARCH PROJECTS

Postgraduate Students

1990	Ying, L-H.	MSc (Qual.)	The Role of Insulin Receptor in Human Hypertension
1990-1993	Zee, R.Y.L.	PhD	Molecular Genetics of Human Hypertension
1995-1999	Nyholt, D.	PhD	Migraine Linkage and Allelic Association Studies
1996-2000	Cook, J.	PhD	Patellar Tendinopathy: Clinical and Imaging Studies
1995-2001	Haupt, L.	PhD	IS-RT PCR Localisation of Matrix Metalloproteinase Gene Expression in Human Breast Cancer
1995-2002	Rutherford, S.	PhD	The Use of Microsatellite Markers to Study Essential Hypertension Genes
1995-2002	Selvey, S.	PhD	Matrix Metalloproteinase Induction and Invasive Breast Cancer
1997-2003	Rogers, K.	PhD	Natural Products Affecting the Human Serotonergic System
1998-2003	Curran, J.	PhD	Novel Genotypes Associated with Sporadic Breast Cancer Development,
1996-2003	Ashton, K.	PhD	Molecular Abberations of Non-Melanoma Skin Cancer and Precursors
1997-2003	Lea, R.A.	PhD	The Role of Ion Channel and Related Genes in the Aetiology of Typical Migraine
2001-2003	Sundholm, J.	MPhil	Mutation Analysis of Two Migraine Candidate Genes
1999-2004	Mellick, A.	PhD	Matrix Metalloproteinases: The Molecular Basis of Malignancy in Breast Carcinomas
2000-2004	Carless, M.	PhD	Molecular Abberations Associated with Non-Melanoma Skin Cancer
1999-2004	Tajouri, L.	PhD	Differential Display of Gene Expression in Multiple Sclerosis
2000-2005	Johnson, M.P.	PhD	Genetic Study of the Human Serotonergic System in Migraine using a pooling method
2001-2005	Simcock, W.	PhD	Parallel Analysis of Gene Expression: Bone Cells as a Model System
2003-2006	Curtain, R.	PhD	Gene Expression Analysis of Migraine
2002-2005	Smith, RA.	PhD	Role of Nuclear Receptor Genes in Sporadic Breast Cancer
2003-2007	Colson, N.J.	PhD	The Role of Hormones and Hormone Related Genes in Migraine
2001-2008	Bellis, C.	PhD	An Investigation of Cardiovascular Disease Genes in

			the Norfolk Island Population
2003-present	Quinlan, S.	MPhil	Analysis of the Effects of Migraine on Male Disability
2005-2009	Szvetko, A.L.	PhD	Determination of gene expression profiles in MS affected brain tissue (MS Society PhD Fellowship)
2005-2009	Hiesh, K.	PhD	Breast cancer genetic analyses
2006-2008	Green, M.	PhD	Lymphoma genome and expression studies
2006-2007	Chikhani, S.	MPhil	The role of GATA 4 in migraine and stroke
2007-present	Gabrovska, P.	PhD	Breast Cancer expression studies
2007-present	Cox, H	PhD	Migraine gene mapping in the Norfolk population
2007-present	Matovinovic, E	PhD	CVD risk trait gene mapping in NI isolate
2008-present	Fowder, J	PhD	Identification of hypertension genes post GWAS
2008-present	Greely, R	PhD	Identifying susceptibility genes for SCC post GWAS
2008-present	Maher, B	PhD	Identification of an X-linked gene involved in migraine and investigation into epilpesy gene that may cause co-mobidity of these disorders
2008-present	Genesan, S	PhD	Interaction of genotype, vitamin status and homocysteine level on migraine severity
2009-present	Bonilla, C	PhD	Gene expression and genomic variation signatures as prognostic indicators to therapeutic response in Diffuse Large B-Cell Lymphoma patients
2009-present	Camilleri, E.	PhD	Defining the Immuno-regulatory role of FOXP Family Members in Non-Hodgkin's Lymphoma
2009-present	McKenzie, J	PhD	Gene expression in multiple sclerosis brain and blood samples
2009-2009	Roy, B	MM	?
2010-present	Benton, M.	PhD	Envirogenomic signatures & risk prediction of Metabolic Syndrome in Norfolk Island population
2010-present	McCarton, C.	PhD	The genetics of coronary artery disease
2010-present	Okpokam, N.	MPh	A GWAS for risk factors assoc w/ bone mineral density & osteoporosis in Norfolk Island isolate.

Honours Students (34 Hons; 21 Hons I, 8 Hons IIA, 2 Hons IIB, 3 current)

1994	Nyholt, D.	Migraine Association Studies Using Chromosome 19 Microsatellite DNA Markers	Hons I
1994	Mitchell, C.	The Analysis of Medicinal Plants Using High Performance Liquid Chromatography (HPLC)	Hons I
1995	Zancola, B.	Genetic Diversity in the Feral and Domestic Cat	Hons I
1995	Van Hofwegen, H.	Detection and Estimation of the Levels of Specific Environmental Contaminants in Medicinal Plants	Hons I
1995	Tran, C.	Laboratory and Field Evaluation of Neem Seed Extracts for the Control of Biting Midges	Hons I
1996	Salzmann, M.	Screening Medicinal Plants for the Presence of Ochratoxins and Organochlorine Pesticides	Hons IIA
1996	Lea, R.A.	A Multiplex Genome Scanning Approach to Mapping Migraine Gene Loci	Hons I
1997	Curran, J.	Molecular Analysis of Breast Cancer Susceptibility Genes	Hons I
1997	Defteros, N.	Mutation Analysis of the Ca^{2+} Channel α_{1A} Subunit Gene CACNL1A4 in Migraine	Hons I
1998	Hutchins, C.	A Hypertension Genome Scan Using Microsatellite Markers in EST Rich Regions	Hons I
1999	Carless, M.	Comparative Genomic Hybridisation of Keratoacanthoma	Hons I
1999	Walker, S.	The Clonality of Non-Melanoma Skin Cancers	Hons I
1999	Jordan, K.	The Role of Human Dopamine Receptor Genes in	Hons IIB

		the Aetiology of Migraine	
1999	Dohy, A.	The Role of LDLR Receptor Genotypes and the Development of Obesity	Hons IIB
2000	Bellis, C.	Development of a Molecular Genetic Technique for Animal Species Identification Validated for use in Forensic Science Casework	Hons I
2000	Lintell, N.	Analysis of Vitamin D and Glucocorticoid Receptor Gene Polymorphisms in Solar Keratosis	Hons IIA
2000	Tatham, N.	A Population Association Study of Calcium Channel Genes and Migraine	Hons I
2000	Wright, K.	DOP-PCR Amplification of Small and Degraded DNA Samples for STR Profiling	Hons IIA
2001	Smith, R.A.	Expression Analysis of Breast Cancer Candidate Genes	Hons I
2001	Gillespie, S.	Molecular Analysis of Solar Keratosis Susceptibility Genes	Hons I
2002	Colson, N.	Investigation of X Chromosomal Migraine Genetic Component	Hons I
2002	Moses, D.	Genetics of Focal and Segmental Glomerulosclerosis and Heart Block	Hons IIA
2004	Kerr, M.	Gabra 3 and migraine associated linkage studies	Hons IIA
2004	Kollar, K.	Association of MMP's in Skin Cancer	Hons IIA
2004	Szvetko, A.L.	Gene Expression in MS	Hons I
2004	Lindley, E.	Colon cancer diagnostics using microsatellite markers	Hons IIA
2005	Kraska, T.	Molecular genetic studies of non-melonoma skin cancer	Hons I
2005	Liu, A.	Pharmacogenetics of candidate migraine susceptibility genes: Dopmaine beta-hydroxylase (DBH), methylenetetrahydofolate reductase (MTHFR) and Angiotensin converting enzyme (ACE)	Hons IIA
2005	Cox, H.	Use of the Norfolk population for migraine gene mapping	Hons I
2006	Gale, J.	Development of new diagnostic tests for familial hemiplegic migriane	Hons1
2007	Grealy, R	Molecular genetics studies of SCC	Hons I
2006-7	Fowder, J.	Hypertension Gene Studies in the NI Population	Hons I
2007	Mationg, E		Hons I
2007	Kuwahata, M		Hons I
2006-7	Gabrovska, P	Gene expression in human breast cancer	Hons I
2008	McKenzie, J	Variation of receptors for estrogen, progesterone, and vitamin D, and CRYAB in MS.	Hons I
2008	Plummer, P	Gene expression of GABA A & B Rec genes in migraine population	Hons IIA
2008	Camilleri, E	DNA MTHFR and Histone deacetylase inhibitors for the treatment of diffuse large B-cell lymphoma	Hons I
2010	Chen, T.	Potential co-morbidity effects of the SCN1A and GABRG2 on FHM and SMEI	Current
2010	Buteri, J.	Association study of CGRP, CGRP receptor and opioid receptor with migraine	Current
2010	Donges, B.	Genetics of Memory: Role of the APOE, COMT and CPEB genes in Prospective and Retrospective Memory in Non-pathological Adults	Current

INVITED SEMINARS

National

Department of Biochemistry, Univ. of N.S.W.
Department of Medicine, Concord Repatriation Hospital.

Department of Medicine, University of Sydney.
Genetics and Epidemiology Unit, University of Melbourne.
Sydney Molecular Biology Group.
Public Health and Tropical Medicine, University of Sydney.
School of Biological Science, Macquarie University.
Medical Genetics Unit, Royal Alexandra Hospital for Children.
School of Biological Sciences, University of Sydney.
Experimental Science Group, Griffith University Gold Coast.
Department of Medicine, Prince Charles Hospital, Brisbane.
Department of Medicine,University of Queensland, Brisbane.
Department of Physiology,University of Queensland, Brisbane.
Department of Medicine, Royal Brisbane Hospital, Brisbane.
Garvan Institute, Sydney.
Neurogenetics Society, Concord Hospital, Sydney.
Australian Society of Neurologists Annual Meeting, Brisbane.
Gold Coast Hospital Centenary Research Conference, Gold Coast.
Flinders Medical Research Institute, Adelaide.
Department of Biochemistry, University of Queensland, Brisbane.
Department of Physiology and Pharmacology, University of Queensland, Brisbane.
Life Sciences, Queensland University of Technology, Brisbane.
Queensland Institute of Medical Research, Brisbane
BioSpecimen Network Meeting, Baker Institute, Melbourne
Neurology Department, Royal Brisbane Hospital, Brisbane
AGRF Scientific Success Forum, University of QLD, Brisbane
Science Writers Association Annual Meeting, Queensland
Murdoch Children's Research Institute, Melbourne
QIMR Seminar Series, Brisbane
Mater Medical Research Institute (MMRI) External Seminars.
HGSA Seminar Serious, various
Princess Alexandra Research Meeting, Brisbane
Janssen-Cilag. Genetics and Management of Migraine. 28/03/06, Incholm Hotel, Brisbane
Discovery Science & Biotechnology, Gene identification and characterisation - diagnostic and therapeutic applications, Stamford Plaze Hotel, Brisbane, 30 May-1 June 2007
AFA Conference for MS Research Australia 15th October 2007, Royal Pines Resort.
Heart Foundation, Use of Norfolk Island population to identify CVD risk genes, Watermark Hotel Gold Coast, 28th November 2007
Gold Coast Health and Medical Research Conference, The Norfolk Island Genetic Isolate: A tool for complex disease gene mapping, Sanctuary Cove, Gold Coast, 2-7 December 2007
Australian Health & Medical Research Congress, Brisbane Convention Centre16-21st Nov 2008
3rd Blackmores Research Symposium, Sydney 29th April – 2nd May 2010
Integria, Nutraceuticals & Functional Foods Symposium, Brisbane 18th June 2010
Translational Research Excellence (TRX) conference, Brisbane 11-13th Oct 2010

International
Biotechnology Development Meeting, Oslo, Norway
Department of Medicine, Duke University, N.C.
Department of Medicine, Kumomoto University, Japan.
Genomics Research Department, GlaxoWellcome, Stevenage, UK
International Headache Congress, Rome, Italy
University of Hawaii, John A Burns School of Medicine, Hawaii
Southwest Foundation for Biomedical Research, October 2005, San Antonio, Texas USA
Pharmacogenomics Conference, Manipal, India, 17-19 March 2007
BIO conference, San Diego, June 2008
The 2nd World Congress on Controversies in Neurology (CONy) Athens, Greece, Oct 2008
The 3rd World Congress on Controversies in Neurology (CONy) Prague, Czech Republic, Oct 2009

Invited by University of Vienna to give seminar presentation "Molecular Genetics of Migraine" 7th Oct 2009, Vienna, Austria.
Invited to Malaysian Medical Research Colloquium to give seminar presentation 28-29th May 2010, Kuala Lumpur, Malaysia

COLLABORATIONS

1986-1989	Dept of Human Genetics, Australian National University (P.G.Board)
1986-1988	Division of Medical Genetics, UCLA Medical Centre (T.Mohandas)
1986-1989	Dept of Histopathology, The Adelaide Childrens Hospital (D.F.Callen)
1983-1989	Genetics Division, Childrens Hospital, Boston (S.Latt)
1987-1989	MRC Clinical and Population Cytogenetics Unit, Edinburgh (V.van Heyningen)
1987	Dept of Human Genetics, Yale University (K.K.Kidd)
1987-1989	Dechema Institute, Frankfurt-am-Main (A.J.Driesel)
1988-1998	Dept of Physiology, University of Sydney (B.J.Morris)
1994-1998	School of Mathematical Sciences, ANU (S.Wilson; J. Wicks)
1993-1998	Dept of Medicine, University of Queensland (M. Eadie, R.Gordon; M. West)
1998-2004	Dept of Statistics, Rockefeller University, New York (J. Ott, D. Nyholt)
1993-2005	Instit Neurological Sciences, Prince of Wales Hospital (P.Brimage, P. Goadsby)
1993-present	QLD Institute of Medical Research (A.Green; D. Nyholt, P. Visscher, S. MacGregor, M. Ghandi)
1997-2005	Molecular Medicine, Dept Medicine, Sydney University (G. Nicholson; J. Dawkins)
1995-present	Gold Coast Hospital (S. Weinstein; T. Kay; N. Grey; A. Parnham)
1993-present	Medical Science, Griffith Uni (J. Headrick; N. Morrison; D. Grice; S Ralph, D Maguire)
1999-present	Clinical Genetics, Royal Childrens' Hospital and University of QLD (J. Macmillan)
1997-2001	Gemini Genomics Inc. Cambridge, UK
1999-2007	GlaxoSmithKline, Stevenage, UK and Melbourne, Australia
2002-2007	Sequenom, San Diego, USA
2003-2008	Corbett Research, Queensland
2005-present	Southwest Foundation for Biomedical Research, USA (J. Blangero, J. Curran, M.P. Johnson, S. Rutherford & M. Carless)
2005-present	ESR Institidute, Wellington, NZ (R.A. Lea)
2005-present	Migco Pharmaceuticals Pty Ltd (Larry Stenswick)
2006-present	Italian National Research Council (F. Gianfrancesco & T. Esposito)
2006-present	Migraine Trust, London (A. MacGregor, A. Frith)
2006-present	Emerillon Ltd, Canada
2006-present	CBio Ltd, Queensland

RESEARCH FUNDING

Total funding: ~$13.6 million
Total external funding: $11.15 million

1985-1988	Nicholson, G.A., **Griffiths, L.R.** and McLeod, J.G. Muscular Dystrophy Association, U.S.A. Gene Mapping of Chromosome 1	US $79,461
1987-1988	Nicholson, G.A., Ross, D.A. and **Griffiths, L.R.** Muscular Dystrophy Association, U.S.A. Construction of neuronal-chromosome specific libraries	US $39,904
1989-1991	**Griffiths, L.R.** and Morris, B.J. NH&MRC	$153,385

	Molecular genetic abnormalities in human hypertension	
1994	**Griffiths, L.R.**, Gaffney, P. T. and Irving, M.G.	$8,000
	National Competitive Grant Support Scheme	
	Molecular genetic basis of essential hypertension.	
1994	**Griffiths,L.R.**	$5,000
	Staff Research Initative Scheme	
	Molecular genetic basis of human high blood pressure	
1994	**Griffiths, L.R.**	$7,604
	Staff Research Initative Scheme	
	Molecular genetics of migraine headaches	
1995-1997	Morris,B.J., **Griffiths, L.R.** and West, M.J.	$405,872
	NHMRC	
	Molecular genetics of essential hypertension	
1995	**Griffiths, L.R.,** Gaffney, P.T. and Goadsby P.J.	$12,000
	National Competitive Grant Support Scheme	
	Molecular genetics of migraine	
1995	**Griffith, L.R.,** Irving, M.G., Gray, B. and Gaffney, P.T.	$37,500
	Major Research Facilities Fund	
	GS-2000 DNA Fragment Analyser	
1995	Morris,B.J.and **Griffiths, L. R.**	$20,000
	Ramaciotti Foundation.	
	Automated Facility for Genome Scanning	
1995-1996	Irving MG and **Griffiths, LR**	$6,750
	Staff Research Initiative Scheme	
	Stromal regulation of invasion and metastasis in human breast cancer	
1996	**Griffiths, L.R.,** and Wilson, S.R.	$14,800
	National Competitive Grant Support Scheme	
	Molecular genetics of migraine	
1996	**Griffiths, L.R.,** Irving, M.G., Gray, A.B., and Gaffney, P.T.	$21,200
	Major Research Facilities Fund	
	Molecular Equipment	
1997-1999	**Griffiths, L.R**., Haupt, L, Irving, M.G, Thomspon, E.W.	$126,000
	Kathleen Cunningham Foundation (Aust. Cancer Fund)	
	Matrix metalloproteinase expression in human breast cancer.	
1997	**Griffiths, L.R**	$37,870
	Government Employees Medical Research Fund	
	The role of serotonin related genes in migraine aetiology	
1997-2000	**Griffiths, L.R.**	$2,037,330
	Gemini Research Ltd	
	Molecular genetic analysis of human hypertension	
1998-2000	**Griffiths, L.R.**	$217,971
	NHMRC	
	The role of serotonin related genes in migraine aetiology	
1998	**Griffiths, L.R.**	$12,000
	Griffith University Research Grant	
	Molecular aberrations associated with solar keratoses development	
1998	**Griffiths, L.R.**	$49,500
	Griffith University Research Infrastructure Scheme	
	ABI Prism Genetic Analyser	
1998	**Griffiths, L.R.** & A. Lewis	$260,000
	ARC Research Infrastructure Equipment and Facilities Grant (RIEFP)	
	Qld High Performance Computing Meta-Centre Pilot Project.	
1998-2001	**Griffiths, L.R.**	$1,497,925
	GlaxoWellcome Ltd	
	Molecular genetics of migraine headaches	
2000-2001	**Griffiths, L.R.**	$66,454

	GlaxoWellcome Ltd Molecular genetics of migraine - additional work	
2001-2003	**Griffiths, L.R.** NHMRC High resolution mapping of genomic regions implicated in migraine	$390,000
2001	**Griffiths, L.R.** GlaxoSmithKline Migraine SNP Typing	$26,353
2001-2002	**Griffiths, L.R.** GlaxoSmithKline Molecular genetics of migraine - Extension Studies	$613,260
2001	**Griffiths, L.R.** and Plumas, J. Australian French Embassy Research Exchange Molecular and Immunological Studies of MS and Lymphoma	$13,000
2001	**Griffiths, L.R.,** Headrick, J., Morrison, N.A., Beacham, I.R., Korolik, V. Griffith University Research Infrastructure Program Microarray Gene Scanner	$93,900
2001	Morrison, N.A., Beacham, I.R., Korolik, V., **Griffiths, L.R.**, Headrick, J. and Perkins, A. Griffith University Research Infrastructure Program Facility for analysis of gene expression using real time quantitative DNA amplification	$100,000
2001-2002	Headrick, J.P. and **Griffiths, L.R.** National Heart Foundation Regulation of Myocardial Gene Expression by Adenosine Receptors	$72,000
2001-2002	**Griffiths, L.R.** Rebecca L. Cooper Medical Research Foundation Limited Gene Expression Analysis of Multiple Sclerosis	$16,000
2001-2002	**Griffiths, L.R.** Griffith University Research Development Grant Scheme Gene Expression Analysis of Multiple Sclerosis	$22,310
2001-2002	**Griffiths, L.R** Griffith University Research Infrastructure Program Microarray Facility	$270,000
2002	Rose'Meyer, R., and **Griffiths, L.R.** Griffith University Research Grant Scheme A study into the mechanisms causing age-related reductions in vascular adensosine receptor function	$24,000
2002-2003	**Griffiths, L.R.,** Gough, I., Wetzig, N and Pyke, C. The Wesley Research Institute Foundation Characterisation of Genes Associated with Sporadic Breast Cancer	$143,880
2003-2004	**Griffths, L.R.** Sequenom, Inc Mapping genes in hypertension	$43,000
2003-2004	**Griffths, L.R.** Gene DT Ltd. Cancer Diagnostics	$20,000
2003-2004	**Griffiths, L.R**., Lea, R.A. and MacMillan, J. Brain Foundation Migraine and Stroke: Are There Common Risk Factors?	$10,000
2004-2005	**Griffiths, L. R.** NHMRC Equipment Grant Sanyo VIP Series Ultra low temp upright freezer & freezer storage system (12 x URO 462 FB systems and 12 x URO 452 FB systems)	$32,049
2004-2005	**Griffiths, L.R.,** Lea, R.A. & MacMillan, J. Brain Foundation	$15,000

	The Role of the Estrogen Receptor Gene in Migraine	
2004-2005	**Griffiths, L.R.** & Fernandez, F. Griffith University Encouragement Grant Analysis of gene expression patterns in MS	$15,000
2004-2005	**Griffiths, L.R.** & Lea, R.A. Griffith University Research Grant Use of the Norfolk Island isolate to identify genetic risk factors involved in CVD	$16,000
2004-2005	Crane, D.I., Clarke, F.M., Burns, D, Hughes, J, & **Griffiths, L** GURIP Capillary Analyser for the GU DNA Sequencing Facility	$125,000
2005	**Griffiths, L.R.** CBio Ltd MS Clinical Trial Laboratory Analysis	$33,000
2004-2007	**Griffiths, L.R.**, Lea, R.A. & Lewis, A.. ARC Linkage Development of improved technologies for high throughput screening of potential disease susceptibility genes.	$258,150
2005-2007	**Griffiths, L.R.** CBio Ltd+3300+ Gene Expression Studies on Multiple Sclerosis	$335,844
2007	**Griffiths, L.R.** Emerillon Ltd Migraine channel gene studies	$50,000
2006-2007	**Griffiths L.R.**, Blangero, J. & Lea, R.A. National Heart Foundation Use of the Norfolk Island isolate to identify genetic risk factors for cardiovascular disease	$110,000
2006-2007	**Griffiths, L.R** & Nyholt, D. QIMR-GU Seed Funding Migraine EST & PGR Gene Analysis	$30,000
2006	**L.R. Griffths** MediGard Evaluation of retractable syringe prototype	$2,000
2006	**Griffiths, L.R.**, Lea, R.A. & MacMillan, J. Brain Foundation The interaction of genotype, vitamin status and homocysteine level on migraine severity	$18,000
2006-2007	**Griffiths, L.R.** and Colson, N.J. GlaxoSmithKline Postgraduate Support Grant (Natalie Colson) The role of hormonal and vascular genes in migraine susceptibility	$30,000+
2007	Prof JS Mattick; Prof MA Ragan; Prof BM Degnan; Prof V Brusic; Dr MJ Pheasant; Dr CA Wells; **Prof LR Griffiths**; Dr JM Hogan; A/Prof P Roe; Prof P Timms; Dr BP Dalrymple ARC LIEF (LE0775726) Australian Mirror of the UCSC Genome Database and Browser	$306,270
2007	Visscher, P.M. & **Griffiths, L.R.** GMRC Research Collaborative Scheme New methods to map disease genes in an admixture founder population	$34,822
2007	Fernandez, F. and **Griffiths, L.R.** Griffith University New Researchers Grant (NRG) Scheme Investigation of the role of GABA related genes in migraine	$10,000

2007	**Griffiths LR**, Lam A, Crane D, Broadley S, Wells C, Stadlin A, Morrison N, Tajouri L, Fernandez F, Lewohl J & Smith R. GURIP internal grant for 3130 Applied Biosystems 3130 Genetic Analyzer and PCR clean chambers	$100,000
2006-2008	**Griffiths, L.R**., Blangero, J. & Lea, R.A NHMRC Medical Bioinformatics, Genomics & Proteomics Project Use of the Norfolk Island Genetic Isolate for Disease Gene Mapping.	$978,500
2006-2008	**Griffiths L.R.** & Green M. Scholarship stipend from Anthony Herbert for Michael Green's PhD candidature ($25Kpa for 3yrs)	$75,000
2008	**Griffiths, L.R.** & Gandhi, M. QIMR-GMRC Research Collaboration Scheme The Griffith/QIMR Diffuse Large B Cell Lymphoma Project	$20,000
2008	**Griffiths LR**, Neuzil J, Headrick J, Lewohl J, Ashton K, Lam A, Broadley S, Smith R. GURIP internal grant for Nucleic Acid Preparation and Visualisation Workstation	$60,000
2008	**Griffiths LR.** GU encouragement grant Identification of genes influencing CVD risk and migraine via expression profiling in the Norfolk Island pedigree	$15,000
2008	Bequest for Cancer Research (unspecified)	$340,000
2009	Mellick A.S. & **Griffiths L.R.** ARC Discovery Project The role of small non coding RNAs in bone marrow mediated tumour angiogenesis.	$127,000
2009	**Griffith L.R.** QLD International Fellowhip An international strategy to identify the genes involved in migraine	$30,000
2007-2010	Kilpatrick, T., Perreau, V., Foote, S.J., **Griffiths, L.R.,** Moscato, P.A., Scott, R.J., Stankovich, J.M., Rubio, J.P., Bahlo, M., Booth, D.R., Butzkueven, H., Heard, R., Lechner-Scott, J., Wiley, J.S. ARC Linkage Project Identifying genes that influence clinical course and susceptibility in multiple sclerosis.	$400,000
2008-2010	MacGregor, A & **Griffiths, L.R**. Migraine Trust UK. Menstrual Migraine Studies	£38,767
2008-2010	**Griffiths L.R.** Clinical Trial for Migraine (MigCo Pharmaceuticals) Project Consultancy Protocol Development	$15,950
2009-2010	**Griffiths L.R.** & Lea R.A. Nutricia Research Foundation Grant Interaction of genotype, homocysteine and vitamin levels on migraine frequency and severity	$89,314
2009-2010	Gandhi M (QIMR) & **Griffiths L.R.** Cancer Coucil Queensland Project Grant 2 years Biomolecular profiling in PET/CT directed diffuse large B cell lymphoma	$164,000
2010	L.R.Griffiths, Lea R.A., Morrison N., Broadley S. et al. GURIP internal grant for Illumina Bead Array Reader	$100,00

Current Funding

2009-2011	**Griffiths L.R.,** Lea R.A., Goring H., Curran J. & Blangero J. NHMRC Project Grant 3 years Use of expression profiling to identify genes influencing carsdiovascular risk in the NI population isolate.	$671,500

2009-2011	**Griffiths L.R.** Intl Science Linkages, from Dept Innovation, Sci & Research An intl strategy to identfy the genes involved in migraine	$341,543 AUD
2009-11	A. Macgregor **& L.R.Griffiths** Merck, Sharp & Dohme (MSD) A case-control study of the molecular genetics of menstrual migraine	£79,275
2010-2011	**Griffiths L.R.** Corbett Philanthropic support "Molecular Genetic Research" incl postdoctoral salary (2 yrs) and PhD stipend (3 years)	$200,000
2011-2015	**Griffiths L.R., Neuzil J. Haupt L.** Philanthropic donation from Clem Jones Estate in support of "Mesenchymal Stem Cell Research"	$2M
2011	**Griffiths L.R.** (Gold Coast Node) ARC EIF Super Science Initiative – Translating Health Discovery Grant: A QLD node of Translating Health Australia ($700K for GHI/GRC)	$12.5M
2011-2014	Griffiths L.R., Lea R.A., Chambers S., Youl P. ASI Biobank Project: GU Strategic Investment Funds A genetic approach to investigate clinical & psychosocial outcomes for women with breast cancer.	$389,700

Scholarship/Fellowship Funding

2009-2011	Multiple Sclerosis Research Australia – Postgraduate scholarship to Jason Mackenzie (supervised by **Lyn R. Griffiths)** "Investigation of	$78,000
2010-2012	NHMRC Postgraduate Scholarship to Emily Camilleri (supervised by **Lyn R. Griffiths)** Defining the immuno-regulation role of FOXP family members in Non-Hodgkins lymphoma	$56,188
2006-2008	Use of the Norfolk Island Genetic Isolate for Migraine Disease Gene Mapping NHMRC "Dora Lush" Postgraduate Scholarship to Hannah Cox	$73,833
2005-2007	Use of the NI genetic isolate for migraine disease gene mapping. MS Society PhD Fellowship (Attila Szvetko) Determination of gene expression profiles in MS affected brain tissue	$58,000
2005-2007	GU Postdoctoral Fellowship (Dr Lotti Tajouri) Molecular Genetic Studies of Multiple Sclerosis	$55,000pa

Grants Pending:

NHMRC APP1024735 Project Grant "Use of epigenetic profiling to identify genes influencing cardiovascular risk in the Norfolk Island population isolate." 3 years $ CIA

NHMRC APP1024737 Project Grant "Variation in the mitochondrial genome and risk of metabolic disease traits in the isolated population of Norfolk Island" 3 years CIA $

NHMRC APP1024738 Project Grant "Identifying the genetic cause of FSGS and complete heart block in an affected Australian family" 2 years $ CIA

NIH Grant "Genetic basis for nutraceutical therapy of migraine with aura". PA-10-006, "Mechanisms, Models, Measurement, & Management in Pain Research (R01)". 2011- 2015 $1,277,540AUD

ARC – Discovery Grant with David Shum
NIH Grant with Sue Rutherfor Seigel

MSRA – 23K in Year 1 for Lyn Griffiths: Incubator

PATENTS

1997	**Griffiths, L.R.** United States Patent No: 5,688,647 Detection of dinucleotide repeat polymorphism in exon 18 of LDL receptor gene for determining predisposition to obesity.
2000	**Griffiths, L.R.**, Rutherford, S. and Morris, B. United States Patent No: 6,156,510 Polymorphisms in a microsatellite region of a glucocorticoid receptor gene. (Gemini Genomics Ltd Licensed)
2001	**Griffiths, L.R.** Patent Application: PCT/GB99/01450 Polymorphism in a Nitric Oxide Synthase Gene (Gemini Genomics Ltd Licensed)
2004	**Griffiths, L.R.,** Lea, R.A., Colson, N.J. Provisional Patent Filed: September 2004 PCT/AU2004/001248 Patent Application: PCT for Hormone Receptor Genes & Migraine Susceptibilty (MigCo Ltd Licensed) (GU Ref : 12536PC2-MLE)
2008	**Griffiths, L.R,** Lea, R., Fernandez, F. Provisional Patent Filed: December 2008 PCT/AU2008/000877 Patent Application: Dopamine-Beta-Hydroxylase Genetic Polymorphism And Migraine (GU Ref:18829PC1-MLE)
2010	**Griffiths, L.R.,** Lea, R, Cox, H.C. Provisional Patent Filed: Semtember 2010 PCT/AU2010/903979 Prioritised genetic polymorphisms and migraine susceptibility (Patent Attorney Ref No: 22476AU1-DEC/EAL)
In Prep 2011	Identification of disease signatures using a new bioinformatic approach.

PROFESSIONAL SOCIETIES

Member	Australian Society for Medical Research
Member	American Society Human Genetics
Member	Australian Society for Biochemistry and Molecular Biology
Member	High Blood Pressure Research Council of Australia
Member	Australian Headache Society
Member	Human Genetics Society of Australasia
President	HGSA Queensland Branch
Member	International Congress for Human Genetics SPC 2011

PROFESSIONAL APPOINTMENTS

Director	Australian Society for Medical Research	2000-2001
Convenor	Australasia Gene Mapping Conference, Cairns	July 2001
Convenor	ASMR National Conference, Gold Coast	Nov 2001
Member	Planning Committee Australasian GeneMapping Conference, Hobart	2002
Member	Curriculum Planning Group, School of Medicine, Yr 1 & 2	2004-2005
Member	Council of the Queensland Institute of Medical Research	2002-present
Chair	Scientific Program Committee, 11th ICHG, Brisbane Aug 2006	2003-2006

Member	Griffith University Innocence Project Advisory Board	2003-present
Member	Griffith University Pharmacy Advisory Board	2004-present
Chair	Griffith Health Research Committee	2004-present
Member	Ministerial Health & Medical Research Committee	2004-2006
Member	Gold Coast Hospital Foundation Board	2006-present
Member	CNN Future Summit Board of Directors	2006-present
Member	E-Health Research Centre Advisory Committee (CSIRO & QLD Govt.)	2006-present
Member	NHMRC Biomedical Training Fellowships Assessment Panel	2006
Member	Australian-US Fulbright Commisson Fellowships Assessment Panel	2006-present

SERVICE

Head, School of Health Science, Griffith University	1995 - 2000
Director, Genomics Research Centre, Griffith University	1997 - present
Acting Deputy Dean (Research), Applied Science, Griffith Uni	Aug - Oct, 1994
Deputy Dean Staffing, Health Science, Griffith Uni	1995
Deputy Dean (Research), NHS Faculty	1996 - July 1997
Chair, Health Science School Board/Committee	1995 - 1999
Chair, Planning Committee, BHSc Honours Course, Health Science	
Honours Course Coordinator, Health Science	1996
Chair, Faculty Research and Postgraduate Studies Board,	1996 - July 1997
Member, Planning Committee, Grad Dip., Genetic Counselling	1996
Director, Siemens Science School, Griffith University, Gold Coast	1994 - 1997
Director, Environmental Analysis and Research Laboratory, GUGC	1995 - 1999
Member, Faculty Standing Committee	1995 - 1997
CSIRO Student Exchange Scheme, Project Organiser	1993 - 2005
Distinguished Speaker Program	1994 - 1996
Invited Speaker, various Rotary, Zonta Lion's Clubs	1995 - present
Work Experience, 45 students	1993 - 2001
Invited Speaker, Migraine Support Groups	1997 - present
Invited Speaker, Queensland Museum Public Lecture Series	1995 - 1998
Invited Speaker, Australian Brain Foundation Conferences	1995, 2002
Invited Speaker, Gold Coast Stroke Support Group	2002
Invited Speaker, Heart Foundation Fundraising events	2007
Invited Speaker, MS Society Fundraising events	2007
Member, Griffith SAFE Change Management Project	2006
Griffith Health Group Board Representative	2006
Head, School of Medical Science, Griffith University	2004-2007
Council Member, Qld Institute Medical Research Council	2004-present
Member, Somerset College Board	2006-present
Board Member, Gold Coast Hospital Foundation	2006-present

RESEARCH OVERVIEW

Grants

71 Successful (25 NCG, 7 Industry)

Students

Postgraduate: 27 completed, 24 PhD, 3 MPhil - 14 Current
Honours: 38 completed, 27 Hons I, 9 Hons IIA, 2 Hons IIB - 0 Current

Publications

196 (refereed and published or in press)
3 refereered book chapters
14 (submitted, under review)

THESES

BSc Honours Thesis: Leigh's Disease: Biochemical Studies.
PhD Thesis: Chromosome 1 Gene Mapping with reference to Charcot-Marie-Tooth Disease.

PUBLICATIONS - Refereed

H index: (2003-2008) 15 [25 for 1996-2008] As at 31st Jan 2011 H = 31, Citations Total = 2487
No. citations (2003-2008) 2139

189 papers published in international journals, after regular submission and review.
(Plus 361 abstracts: 225 Australian scientific meetings, 104 International scientific meetings.)

1980

1. Schofield, P.J., **Griffiths,L.R.**, Rogers,S.H. and Wise,G.(1980) An improved method for the assay of platelet pyruvate dehydrogenase. *Clin.Chim. Acta* 108: 219-227.

1982

2. Nicholson, G.A. and **Griffiths, L.R.** (1982) Acetylcholine receptor antibody in the diagnosis and management of myasthenia gravis. *Clin.Exp.Neurol.*.18: 61-69.

1983

3. Nicholson, G.A. and **Griffiths, L.R.** (1983) A sensitive assay for creatine kinase in serum samples dried on paper: enhanced thermal stability of the dried enzyme. *Pathology* 15: 21-25.
4. Nicholson, G.A. and **Griffiths, L.R.** (1983) Comparison of diagnostic tests in myasthenia gravis. *Clin. Exp. Neurol.* 19: 45-49.
5. Nicholson, G.A., McLeod,J.G. and **Griffiths,L.R.** (1983) The acetylcholine receptor antibody in the diagnosis of myasthenia gravis. *Med. J. Aust.* 2: 334-337.

1987

6. **Griffiths, L.R.,** Nicholson, G.A., Ross, D.A., Zwi, M.B., McLeod, J.G., Mohandas, T., and Morris, B.J. (1987) Regional chromosomal assignment of human renin gene to 1q12->qter and use in linkage studies in Charcot-Marie-Tooth disease. *Cytogenet. Cell Genet.* 45: 231-233.

1988

7. **Griffiths, L.R.**, Zwi, M.B., McLeod, J.G. and Nicholson, G.A. (1988) Chromosome 1 linkage studies in Charcot-Marie-Tooth neuropathy Type 1. *Am. J. Hum. Genet.*(IF 12.340) 42: 756-771. **(4 Citations)**

8. Morris, B. J. and **Griffiths, L. R.** (1988) Frequency in hypertensives of alleles for a RFLP associated with the renin gene. *Biochem. Biophys. Res. Comm.* 150: 219-224.
9. **Griffiths, L.R.**, Ross, D.A., Mesterovic, N., McLeod, J.G. and Nicholson, G.A. (1988) A chromosome 1 *Bgl*I RFLP for the LR67 anonymous DNA segment (DIS26). *Nuc. Acids Res.* (IF 7.260) 16: 7752.

1989

10. **Griffiths, L.R.**, Zwi, M.B., McLeod, J.G., Ross, D.A. and Nicholson, G.A. (1989) Heterogeneity evidence and linkage studies on Charcot-Marie-Tooth disease. *Neurolog y* (IF 5.973) 39: 280-281.
11. **Griffiths, L.R.**, Board, P.G., Zwi, M.B., Morris, B.J., McLeod, J.G. and Nicholson, G.A. (1989) The B subunit of coagulation factor XIII is linked to renin and the Duffy blood group to alpha-spectrin on human chromosome 1. *Hum. Heredl.* (IF 3.176) 39: 107-109.

1990

12. **Griffiths, L.R.**, Zwi, M.B., McLeod, J.G. and Nicholson, G.A. (1990)Linkage studies on hypertrophic motor and sensory neuropathy type 1. In: *Neurology & Neurobiology vol. 53. Charcot-Marie-Tooth Disorders: Pathophysiology, Molecular Genetics and Therapy*, Eds Lovelace, R.E. and Shapiro, H.K., Alan R. Liss, Inc., New York, pp 269-277.
13. **Griffiths, L.R.**, Zwi, M.B., Mesterovic, N., Ross, D.A., Board, P.G., Callen, D.F., Mohandas, T., Buckland, R., Fletcher, J. M., McLeod, J.G. and Nicholson, G.A. (1990) Isolation and use of chromosome 1 probes for linkage studies on Charcot-Marie-Tooth disease. *Ann. Hum. Genet.* (IF 2.680) 54: 31-37.

1991

14. **Griffiths, L.R.**, Zee, R.Y.L., Ying, L-H. and Morris, B.J. (1991) A locus on the long arm of chromosome 1 as a possible cause of essential hypertension. *Clin. Exp. Pharmacol. Physiol.* (IF 1.672) 18: 363-366.
15. Zee, R.Y.L., Ying, L-H. , Morris, B.J. and **Griffiths, L.R.** (1991) Association and linkage analyses of restriction fragment length polymorphisms for the human renin and antithrombin III genes in essential hypertension. *J. Hypertens* (IF4.871) 9: 825-830.
16. Ying, L-H. , Zee, R.Y.L., **Griffiths, L.R.** and Morris, B.J. (1991). Association of an RFLP for the insulin receptor gene, but not insulin, with essential hypertension. *Biochem. Biophys. Res. Comm.* 181: 486-492.

1992

17. Zee, R.Y.L., Lou, Y.K., **Griffiths, L.R.** and Morris, B.J. (1992). Association of an insertion/ deletion polymorphism of the angiotensin I-converting gene with essential hypertension. *Biochem. Biophys. Res. Comm.* 184: 9-15.
18. Zee, R.Y.L., Morris, B.J. and **Griffiths, L.R.** (1992). Association analyses of RFLPs for the α_2 and β_1-adrenoceptor genes in essential hypertension. *Hypertens. Res.* (IF 1.731) 15:57-60.
19. Zee, R.Y.L., **Griffiths, L.R.** and Morris, B.J. (1992). Marked association of a RFLP for the low-density lipoprotein receptor gene with obesity in essential hypertension. *Biophys. Res. Comm.* 189: 965-971.

1993

20. Ying, L-H. , Zee, R.Y.L., **Griffiths, L.R.** and Morris, B.J. (1993). Non-linkage of insulin receptor locus with essential hypertension in an affected pedigree. *Hypertens. Res.* (IF 1.731) 16:25-28.

21. Morris, B.J., Zee, R.Y.L., Ying, L-H.and **Griffiths, L.R.** (1993). Independent, marked associations of alleles of the insulin receptor and dipeptidyl carboxylase 1 genes with essential hypertension. *Clin. Sci.* (IF 2.168) 85: 189-195.
22. Zee, R.Y.L., Lou, Y.K., **Griffiths, L.R.** and Morris, B.J. (1993). Molecular genetic analyses of RFLPs for PCR-amplified growth hormone gene, renal kallikrein gene and atrial natriuretic factor gene in essential hypertension. *Hypertens. Res.*(IF 1.731) 16:113-120.

1995

23. Zee, R.Y.L., Schrader, A.P., Robinson, B.G., **Griffiths, L.R.** and Morris, B.J. (1995). Association of *Hin*cII RFLP of low density lipoprotein receptor gene with obesity in essential hypertensives. *Clin.Genet.* (IF 2.367) 47:118-121.
24. **Griffiths, L.R.**, Nyholt, D.R., Curtain R.P., Gaffney, P.T. and Morris B.J. (1995) Cross-sectional study of a microsatellite marker in the low density lipoprotein receptor gene in obese normotensives. *Clin. Exp. Pharmacol & Physiol* (IF 1.672) 22:496-498.

1996

25. Friend, L.R., Morris, B.J., Gaffney, P.T., and **Griffiths, L.R.,** (1996) Examination of the role of nitric oxide synthase and renal kallikrein as candidate genes for essential hypertension. *Clin Exp. Pharmacol and Physiol* (IF 1.672) 23: 564-566
26. Haupt, L.M., Thompson, E.W., **Griffiths, L.R.** and Irving, M.G., (1996). *IS*-RT-PCR Assay detection of MT-MMP in a human breast cancer cell line. *Biochem Mol Biol Intl* 39:553-561
27. Nyholt, D.R., Curtain, R.P., Gaffney, P.T., Brimage, P, Goadsby P.J. and **Griffiths L.R.** (1996) Migraine association and linkage analyses of the human 5-hydroxytryptamine ($5HT_{2A}$) receptor gene. *Cephalagia* (IF 3.133) 16: 463-467.

1997

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173. R.A. Smith, P. Gabrovska, R.A. Lea, S.R. Weinstein and **L.R. Griffiths** 2010 Detection of mRNA for nuclear receptor co-activators 1 and 3 in archival breast cancer tissue and surrounding stroma: A tissue expression study. *Open Breast Cancer Journal*. 2: 60-65.
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186. Moradi M., Kirk E., Feneley M., Winlaw D., Posch M.G., Marinson J., Blue G., Fatkin D., **Griffiths L.R.** and Butler T. (2011) Investigation of Association between PFO Complicated by Cryptogenic Stroke and a Common Variant of the Cardiac Transcription Factor GATA4. *PLoS ONE* (Accepted 9th May 2011).

ANZgene Consortium publications:

187. Bahlo, M., Booth, D.R., Simon A Broadley, Brown, M.A., Foote, S.J., **Griffiths, L.R.,** Kilpatrick, T.J., Lechner-Scott, J., Moscato, P., Perreau, V.M., Rubio, J.P., Scott, R.J., Stankovich, J., Stewart, G.J., Taylor, B.V., Wiley, J., Clarke, G., Cox, M.B., Csurhes, P.A., Danoy, P., Drysdale, K., Field, J., Greer, J.M., Guru, P., Hadler, J., McMorran, B.J., Jensen, C.J., Johnson, L.J., McCallum, R., Merriman, M., Merriman, T., Pryce, K., Tajouri, L., Wilkins, E.J., Browning, B.L., Browning, S.R., Perera, D., Broadley, S., Butzkueven, H., Carroll, W.M., Chapman, C., Kermode, A.G., Marriott, M., Mason, D., Heard, R.N., Pender, M.P., Slee, M., Tubridy, N., Willoughby, E. 2009 Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. ***Nature Genetics ERA A** (IF 25.556)* 41(7): 824-828. (53 citations)
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191. Jensen C.J., Stankovich J., Van der Walt A., Bahlo M., Taylor B.V., Van der Mei I.A.F., Foote S.J., Kilpatrick T.J., Johnson L.J., Wilkins E., Field J., Danoy P., Brown M.A., (ANZgene incl **Griffiths L.R.**)*, Rubio J.P. and Butzkueven H. 2010 Multiple sclerosis susceptibility-associated SNPs do not influence disease severity measures in a cohort of Australian MS patients. *PLoS One* (IF 4.38) (Published 2nd April) 5(4):e10003

192. Melanie Bahlo, Jim Stankovich, Patrick Danoy, Peter F Hickey, Sharon R Browning, (ANZgene MS Consortium incl **Lyn R. Griffiths**)*, Matthew A Brown, Justin P Rubio. 2010 Saliva-derived DNA performs well in large-scale, high-density SNP microarray studies. *Cancer Epidemiology, Biomarkers & Prevention* (IF 4.9) 19(3):794-798
193. Riveros C., Mellor D., Kaushal S. Gandhi, McKay F.C., Cox M.B., Berretta R., Yahya Vaezpour S., Inostroza-Ponta M, Broadley S., Heard R.N., Vucic S., Stewart G.J., Williams D.W., Scott R.J., Lechner-Scott J., Booth D.R., Moscato P., ANZgene Multiple Sclerosis Genetics Consortium incl **Griffiths L.R.** 2010 A Transcription Factor Map as revealed by a genome-wide Gene Expression Analysis of whole-blood mRNA Transcriptome in Multiple Sclerosis. *PLoS One* (IF 4.38) 2010 Dec 1;5(12):e14176.
194. Field J., Browning S.R., Johnson L.J., Danoy P., Varney M.D., Tait B.D., Gandhi K.S., Charlesworth J.C., Heard R.N., ANZgene Multiple Sclerosis Genetics Consortium (incl **Griffiths L.R.**) et al. 2010 A polymorphism in the *HLA-DPB1* gene is associated with susceptibility to multiple sclerosis. *PLoS* One (IF 4.38) 2010 Oct 26;5(10):e13454.
195. Patsopoulos N. A., Esposito F., Ottoboni L., Reishl J., Bauer D. et al. Incl the ANZgene Consortium with **Griffiths L.R.** 2010 Genomewide meta-analysis identifies *EOMES* and other novel MS susceptibility loci. *Annals of Neurology* (IF 9.6) (Accepted August 10 2010)
196. O'Gorman C., Freeman S., Taylor B.V., Butzkueven H., ANZgene Consortium., Broadley S.A. (**Griffiths L.R.** in acknowledgements) (2011) Familial recurrence risks for multiple sclerosis in Australia. *JNNP* (Published online May 7 2011).

Publication Highlights

- Association of a Notch 3 gene polymorphism with migraine susceptibility, *Cephalalgia*, 2010 Sep 2 was selected for Faculty of 1000 Medicine (www.f1000medicine.com) and evaluated by Joost Haan see http://www.f1000medicine.com/article/d9mgvj5x55s5429/id/5115959
- Australasian Science Magazine March 2010 "Migraine relief from vitamin supplement".
- Australasian Life Scientist Magazine July 2009 "Genetic Headache".

CONFERENCE PAPERS – 376 abstracts, 113 International and 263 National

SELECTED MEDIA COVERAGE

Newspaper Articles

7-8 May 1994	The Weekend Australian	"Gene researchers put heads together on migraine"
Feb 1995	Reader's Digest	Migraine Research
Oct 1995	Campus Review	"Unis share $290m in largest NHMRC round"
3 Feb 1996	The Sydney Morning Herald	Hypertension Genetics
Mar 1996	Courier Mail	Migraine Research
12 May 1997	Sydney Morning Herald	Migraine Research
3 July 1998	Innovations Magazine	Migraine Research
28 Nov 1998	Good Weekend	Migraine Research
9 Mar 1999	The Courier Mail	"$1.5m to track migraine gene"
6 May 2000	New Scientist	"Genetic Bounty"
15-16 Apr 2000	Weekender	"Genetic Bounty"
Sept/Oct 2003	Today's Life Science	"Migraine Gene Quest"
6 April 2002	The Australian	"Third gene found, but migraines still a mystery"
11 July 2003	The Melbourne Age	"Research offers hope for Migraine sufferers"
4 August 2009	Australasian Science	(Editor - Guy Nolch) "Migraine relief from vitamin supplement"

Television - Special Programs

2002	National Geographic Discovery Channel	"Gene Hunters" 13 part series, featuring my Norfolk Island Genetic Studies as Episode 1
18 April 2006	CNN International By CNN's Michael Bayand & Matt Ford	The code of life - A CNN Future Summit technology profile "Genes are the basic building blocks of life, and in studying them genetic science is giving us the ability to adapt and alter ourselves fundamentally, providing unprecedented opportunities to improve on nature."
June 2006	Channel 9	"What's Good for You?" series, featuring my Migraine Research in Episode 9

Television – Interviews

May 1994	Ch 9 News Brisbane	Migraine Research
Nov 1996	Cha 9 News	Migraine Gene Localised
Jan 1997	Ch 7 & Ch 9 News	Gemini Research Project
Feb 1997	A Current Affair, Ch 9	Migraine Project
May 1997	National 10 Network	Migraine Research
May 1997	Sydney TCN 9 News	Migraine Research
Mar 1998	Today Tonight	Migraine Research
Feb 2009	Seven Sunrise	Migraine Research – Vitamin B/folate clinical trial

Radio

Media releases such as the ones below have resulted in many radio interviews, and have been aired live on ABC national stations, 4QR (Brisbane), 2NC (Newcastle), 6RN (Perth), 5AN (Adelaide) and local radio stations.

May 2006	Media Release	"Clinical trial of vitamins for migraine relief"
Jun 2004	Media Release	"Genetic link found between hormones and migraine"
Aug 1999	Media Release	"Volunteers to help Hypertension Research"
May 1994	ABC Perth	Migraine Research
May 1994	ABC Sydney	Migraine Research
Jan 1995	2UE Haydn Sargent	Migraine Genetics
Jan 1995	ABC Brisbane Haydn Sargent	Migraine Genetics
Mar 1996	ABC National	Migraine Research
Jan 1997	ABC Radio News	Migraine Project
May 1997	ABC Radio (Aus wide)	Migraine Research
Dec 1997	ABC Radio National	Gene Research Obesity
May 1998	ABC News	Migraine Research
Mar 1999	91.7 Gold FM	$1.5m funding Glaxo-Wellcome
Mar 1999	2RN (National)	Migraine Research

Media Coverage 2010

Subject	Griffith talent	School	Media Outlet	Media Type	Date	Page
Migraine research	Lyn Griffiths	GHI	Weekend Australian	press	6-Feb	12
Children suffering from migraines	Lyn Griffiths	GHI	ABC News	online	15-Feb	
Children suffering from migraines	Lyn Griffiths	GHI	ABC Sunshine and Cooloola Coasts	online	15-Feb	
Children suffering from migraines	Lyn Griffiths	GHI	ABC Gold and Tweed Coasts	online	15-Feb	
Children suffering from migraines	Lyn Griffiths	GHI	Gold Coast Bulletin	press	23-Feb	10
Migraine Relief from a Vitamin Supplement	Lyn Griffiths	GHI	Australasian Science	magazine	1-Mar	29
Children suffering from migraines	Lyn Griffiths	GHI	ABC 891 Adelaide	radio	11-Mar	
Team Tackles Cancer	Lyn Griffiths	GHI	Gold Coast Sun	press	7-Apr	19
Lyn Griffith Wins Award	Lyn Griffiths	GHI	Weekend Gold Coast Bulletin	press	17-Apr	5
Indigenous migrane treatment	Lyn Griffiths	GHI	Australasian Science	magazine	1-May	9
Genetic links and hormonal changes in relation to Alzheimers	Lyn Griffiths	GHI	2DU Dubbo	radio	7-May	
Migraine research	Lyn Griffiths	MBOD - GRC	Channel 7 - Today Tonight programme	TV	10-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	Also covered on 32 other stations	TV	10-Sep	
Clive Palmer Breakfast	Lyn Griffiths	GHI	ABC Gold Coast & Tweed News - 06:30	radio	20-Sep	
Clive Palmer Breakfast	Lyn Griffiths	GHI	ABC Gold Coast & Tweed News - 07:30	radio	20-Sep	
Clive Palmer Breakfast	Lyn Griffiths	GHI	ABC Gold Coast & Tweed News - 13:00	radio	20-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	ABC 702 Sydney	radio	21-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	Also covered in 12 other regions	radio	21-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	Nature Medicine ERA A*	online publication	26-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	Channel 9 - National Nine News - Perth, Brisbane, Sydney, Darwin, Adelaide, Gold Coast, Melbourne	TV	28-Sep	
Migraine research	Lyn Griffiths	MBOD	Also covered on 8 other stations	TV	28-Sep	

		- GRC				
Migraine research	Lyn Griffiths	MBOD - GRC	ONE, Wellington - Breakfast 07:30	TV	29-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	NBN Gold Coast, Coffs Harbour, Tamworth, Lismore, Central Coast & Newscastle	TV	28-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	GNN - News	online	28-Sep	
Migraine research	Lyn Griffiths	MBOD - GRC	Gold Coast Bulletin	press	29-Sep	9
Faulty gene causing migraines	Lyn Griffiths	MBOD - GRC	Getliving.com	online	5-Oct	
Clem Jones funding	Lyn Griffiths	MBOD - GRC	GNN - News	online	21-Oct	
Migraine research	Lyn Griffiths	MBOD - GRC	Sunday Canberra Times	press	7-Nov	12
GCHMR conference	Lyn Griffiths	GHI	GNN - News	online	26-Nov	
GCHMR conference	Lyn Griffiths	GHI	Albert & Logan News	press	1-Dec	15
GCHMR conference	Lyn Griffiths	GHI	ABC Gold coast & Tweed	radio - See Nov	2-Dec	

Media Coverage 2011

Subject	Griffith talent	Research Program	Media Outlet	Media Type	Date	Page
Migraine research	Lyn Griffiths	MBoD	Sydney Morning Herald	press	12-Mar	23
Volunteers	Lyn Griffiths	GHI	612 ABC Brisbane	radio	14-Mar	
Volunteers	Lyn Griffiths	GHI	ABC National - Life Matters	radio	28-Mar	

EXHIBIT B

Sex hormone receptor gene polymorphisms and migraine: A systematic review and meta-analysis

Markus Schürks, Pamela M Rist and Tobias Kurth

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Sex hormone receptor gene polymorphisms and migraine: A systematic review and meta-analysis

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SAGE

Markus Schürks[1,5], Pamela M Rist[1,2] and Tobias Kurth[1,2,3,4]

Abstract

Background: Data on the association between sex hormone receptor polymorphisms and migraine are conflicting.
Methods: We performed a systematic review and meta-analysis on this topic searching for studies published until August 2009. For each study, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) assuming additive, dominant, and recessive genetic models. We then calculated pooled ORs and 95% CIs.
Results and Conclusion: Among the seven genes targeted, four variants were investigated in multiple studies. Effect estimates from an additive model suggest that the ESR-1 594 G > A (pooled OR 1.37; 95% CI 1.02–1.83) and *ESR-1* 325 C > G (pooled OR 1.16; 95% CI 1.03–1.32) variants are associated with any migraine. This pattern does not differ between migraine with and without aura. In contrast, the *ESR-1* Pvu II C > T and *PGR* PROGINS insert polymorphism do not appear to be associated with migraine. Results were driven by studies among Caucasians and may differ in other ethnic groups.

Keywords

Migraine, sex hormone receptors, polymorphisms, meta-analysis

Date received: 8 October 2009; accepted: 30 January 2010

Introduction

Migraine is a common, chronic disorder characterised by recurrent headache attacks and combinations of gastrointestinal and autonomic nervous system symptoms (1), affecting 10–20% of the population. Up to one-third of migraine patients experience an aura prior to or during the migraine headache.

Population-based, clinical, and physiological studies support an important role for sex hormones in the pathogenesis of migraine. For example, migraine prevalence is 3–4-fold higher among women than men, a subgroup of women suffer from menstrual migraine or menstruation-related migraine, migraine prevalence often changes during pregnancy or after menopause, and both oestrogen withdrawal and changes in oestrogen levels can trigger migraine attacks (2–4). These findings have prompted studies investigating the association of variants in genes coding for proteins in sex hormone receptor pathways and metabolism with migraine.

Gene variants located in the oestrogen receptor 1 gene (*ESR-1*) (5–11), oestrogen receptor 2 gene (*ESR-2*) (11), progesterone receptor gene (*PGR*) (7,8,12), androgen receptor gene (*AR*) (12), follicle stimulating hormone receptor gene (*FSHR*) (11), nuclear receptor interacting protein 1 (*NRIP1*) (11), and cytochrome P450, family 19, subfamily A, polypeptide 1 gene (*CYP19A1*) (11) have been targeted. However, many results were either contradictory, which may be due to differences in ethnicity, sample sizes, and the proportion of migraine with aura (MA) and migraine without aura (MO) among the study populations, or have not been replicated in independent populations.

We sought to summarise the current evidence on the association between variants in genes coding for

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proteins in sex hormone receptor pathways and metabolism and migraine including MA and MO by systematically reviewing the literature and performing a meta-analysis.

Methods

Selection of studies

We followed the guidelines for systematic reviews of genetic association studies (13). Two investigators (MS and PMR) independently searched MEDLINE, EMBASE, and Science Citation Index from inception to August 2009 combining text words and MESH terms, were appropriate, for sex hormones ('hormones' or 'sex hormones' or 'estrogen' or 'progesterone') with terms for genetic variations ('gene' or 'polymorphism' or 'genetic variation') and terms for headache and migraine ('headache' or 'headache disorders' or 'migraine' or 'migraine disorders'). The search terms were combined with the 'explode' feature where applicable. We did not use any language restrictions. In addition, we manually searched the reference lists of all primary articles and review articles.

A priori, we defined the following criteria for inclusion:

1. Studies must have a cross-sectional, case-control or cohort design.
2. Authors must investigate patients with migraine and healthy control subjects.
3. Authors must provide information on genotype frequencies of the investigated polymorphisms or sufficient data to calculate these.
4. In studies with overlapping cases and/or controls, the largest study with extractable data was included.
5. Studies must be published as full articles.

In a first step, two investigators (MS and TK) by consensus identified all studies not meeting any of the prespecified criteria by screening the title and abstracts. These studies were excluded. In a second step, the same investigators evaluated the remaining studies in their entirety. Studies were excluded if they did not meet all criteria.

Data extraction

Two investigators (MS and PMR) independently extracted data from the published studies and entered them in a customised database. Disagreements were resolved by consensus. The extracted data included authors and title of study, year of publication, country of origin, ethnicity of population investigated, setting (clinic vs population), study design, genotyping method, migraine status (any migraine, MA, MO), age and gender of study individuals, study size, allele and genotype frequencies, and information on additional genetic variants as well as gene–gene and gene–environment interactions, if investigated. If not given, genotype frequencies were calculated where possible. We did not contact the authors to collect further information.

Statistical analysis

We first used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sex hormone receptor polymorphisms and migraine assuming additive, dominant, and recessive genetic models. We calculated these for polymorphisms which were investigated in at least two independent study populations. The additive model assumes that the risk for migraine among carriers of the heterozygous genotype is half way between carriers of the homozygous genotypes. While the dominant model assumes that carriers of the heterozygous and homozygous variant genotypes have the same risk of developing migraine compared with carriers of the homozygous wild-type genotype, a recessive model assumes that carrying the homozygous variant genotype is necessary to alter the risk for migraine compared with carriers of the heterozygous and homozygous wild-type genotype. We also determined Hardy–Weinberg Equilibrium (HWE) for the control group in each study. We investigated any migraine, MA, and MO.

We then pooled results from all studies and subsequently stratified analyses by ethnicity and gender where applicable.

We weighted the log of the ORs by the inverse of their variance to obtain pooled relative risk estimates. We ran random-effects models which include assumptions on potential variability across studies. We performed the DerSimonian and Laird Q test for heterogeneity and also calculated the I^2 statistic for each analysis (14). This statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance (25%, low; 50%, medium; 75%, high heterogeneity). We used Galbraith plots to examine visually the impact of individual studies on the overall homogeneity test statistic. We evaluated potential publication bias visually by examining for possible skewness in funnel plots (15) and statistically with the methods described by Begg and Mazumdar (15) and Egger (16). The latter method uses a weighted regression approach to investigate the association between outcome effects (log odds ratio) and its standard error in each study.

We considered a P-value < 0.05 as statistically significant.

All analyses were performed using SAS v.9.1 (SAS Institute Inc, Cary, NC, USA) and STATA v.10.1 (Stata, College Station, TX, USA).

Since we only utilised previously published data, we did not obtain approval of an ethics committee or written informed consent.

Results

Figure 1 summarises the process of identifying eligible studies. After title and abstract evaluation, we had identified nine studies (5–12,17). We excluded one more study (17) after evaluating the remaining articles in its entirety and were left with eight studies for this analysis.

Study characteristics

Seven genes involved in sex hormone receptor pathways and metabolism have been investigated in the identified studies: *ESR-1* (5–11), *ESR-2* (11), *PGR* (7,8,12), *AR* (12), *FSHR* (11), *NRIP1* (11), and *CYP19A1* (11). One study further investigated the methylenetetrahydrofolate reductase gene (*MTHFR*) (9). This gene will not be considered for the present analysis.

Table 1A summarises the characteristics of the eight studies included according to the polymorphisms investigated. Four studies (5 study populations: 2 populations from 1 study (6)) have investigated the *ESR-1* 594 G > A (rs2228480) (6,7,9,10), six the *ESR-1* 325 C > G (rs1801132) (5,7–11), two the *ESR-1* Pvu II C > T (rs2234693) (5,8), two the *ESR-1* 30 T > C (rs2077647) (7,9), and three (4 study populations: 2 populations from 1 study (12)) the *PGR* PROGINS insert (*Alu* insert) polymorphism (7,8,12).

Additional polymorphisms have only been looked at in single studies (Table 1B): various *ESR-1* polymorphisms (7,9), *AR* CAG repeat (12), *FSHR* rs6166 (11), *ESR-2* rs4986938 (11), *CYP19A1* rs10046 (11), and *NRIP1* rs2229741 (11).

For the meta-analysis we have only considered polymorphisms that have been investigated in at least two independent study populations. The data given in 1 (9) of the 2 (7, 9) studies investigating the *ESR-1* 30 T > C polymorphism did not allow calculating genotype frequencies. Hence, we could not determine pooled relative risk estimates and we did not include this polymorphism in our meta-analysis.

Almost all studies were performed in Caucasian populations. One study was in an Indian population (8). Further, most (5,6,8,10–12), but not all (7,9), studies presented results stratified by gender in addition to results for the overall study population.

The allele and genotype frequencies for the investigated polymorphisms for migraineurs and controls in each of the studies are summarised in Table 2.

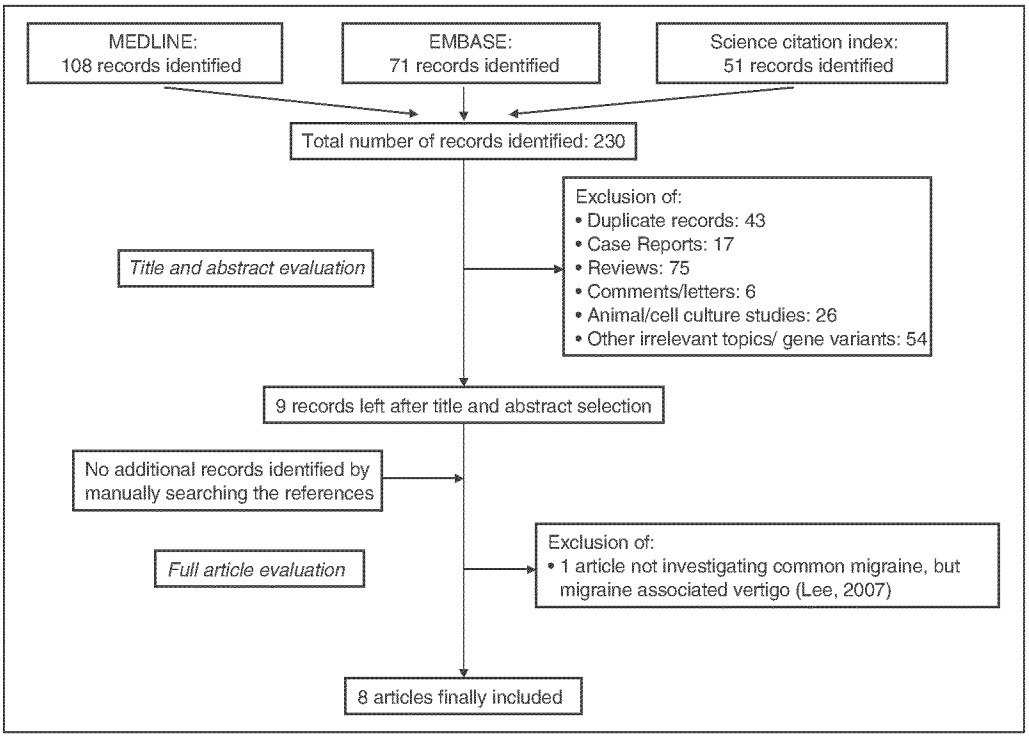

Figure 1. Process of study selection.

Table 1A. Characteristics of the included studies according to the polymorphisms investigated – polymorphisms that have been investigated in at least two papers with extractable data

Reference	Country	Ethnicity	Setting	Gender	Study size with genotypic information				Comment
					Controls	Any migraine	MA	MO	
ESR-1 594 G > A polymorphism (rs2228480)									
Colson (2004) (6)	Australia	Caucasian	Population	Women + men	224	224	139	85	Study population 1 from Colson (6)
				Women	167	167	103	64	
				Men	57	57	36	21	
Colson (2004) (6)	Australia	Caucasian	Population	Women + men	260	260	221	39	Study population 2 from Colson (6)
				Women	224	224	191	33	
				Men	36	36	30	6	
Oterino (2006) (10)	Spain	Caucasian	Clinic	Women + men	232	367	197	170	Other polymorphisms investigated: rs1801132 (*ESR-1* 325 C > G)
				Women	142	286	155	131	
				Men	90	81	42	39	
Kaunisto (2006) (9)	Finland	Caucasian	Population and clinic	Women + men	900	–	898	–	Other polymorphisms investigated: 6 *MTHFR* and 26 *ESR-1* polymorphisms
Corominas (2009) (7)	Spain	Caucasian	NS	Women + men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine. Other polymorphisms investigated: rs1801132 (*ESR-1* 325 C > G), rs2077647 (*ESR-1*), and *PGR* PROGINS insert
Total number of subjects					1826	1061	1541	396	
ESR-1 325 C > G polymorphism (rs1801132)									
Colson (2006) (5)	Australia	Caucasian	clinic	Women + men	249	231	141	75	'Any migraine' also contains 15 patients with 'MA + MO'. Other polymorphisms investigated: rs2234693 (*ESR-1* Pvu II C > T)
				Women	189	167	–	–	
				Men	60	64	–	–	
Oterino (2006) (10)	Spain	Caucasian	Clinic	Women + men	232	367	197	170	Compared to dbSNP and other studies the allele and genotype frequencies in the paper appear flipped because the minus strand instead of the plus strand appears to be used to determine the mutation. Other polymorphisms investigated: rs2228480 (*ESR-1* 594 G > A)
				Women	142	286	155	131	
				Men	90	81	42	39	

(continued)

Table 1A. Continued

Reference	Country	Ethnicity	Setting	Gender	Study size with genotypic information: Controls	Any migraine	MA	MO	Comment
Kaunisto (2006) (9)	Finland	Caucasian	Population and clinic	Women + men	888	–	896	–	Other polymorphisms investigated: 6 *MTHFR* and 26 *ESR-1* polymorphisms
Oterino (2008) (11)	Spain	Caucasian	Clinic	Women + men	372	356	198	158	Compared to dbSNP and other studies the allele and genotype frequencies in the paper appear flipped because the minus strand instead of the plus strand appears o be used to determine the mutation. Other polymorphisms investigated: rs6166 (*FSHR*), rs4986938 (*ESR-2*), rs10046 (*CYP19A1*), and rs2229741 (*NRIP1*)
				Women	263	269	152	117	
				Men	109	87	46	41	
Corominas (2009) (7)	Spain	Caucasian	NS	Women + men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine. Other polymorphisms investigated: rs2228480 (*ESR-1* 594 G > A), rs2077647 (*ESR-1*), and *PGR* PROGINS insert
Joshi (2009) (8)	India	Indian	Clinic	Women + men	217	217	84	133	Other polymorphisms investigated: rs2234693 (*ESR-1* Pvu II C > T) and *PGR* PROGINS insert
				Women	150	150	63	87	
				Men	67	67	21	46	
Total number of subjects					2168	1381	1602	638	
				ESR-1 Pvu II C > T polymorphism (rs2234693)					
Colson (2006) (5)	Australia	Caucasian	Clinic	Women + men	202	231	145	73	'Any migraine' also contains 13 patients with 'MA + MO'. Other polymorphisms investigated: rs1801132 (*ESR-1* 325 C > G)
				Women	140	167	–	–	
				Men	62	64	–	–	
Joshi (2009) (8)	India	Indian	Clinic	Women + men	217	217	84	133	Other polymorphisms investigated: rs1801132 (*ESR-1* 325 C > G) and *PGR* PROGINS insert
				Women	150	150	63	87	
				Men	67	67	21	46	
Total number of subjects					419	448	229	206	

(continued)

Table 1A. Continued

Reference	Country	Ethnicity	Setting	Gender	Study size with genotypic information: Controls	Any migraine	MA	MO	Comment
				PGR PROGINS insert					
Colson (2005) (12)	Australia	Caucasian	Clinic	Women + men	216	232	144	88	Study population 1 from Colson (12). Other polymorphisms investigated: CAG repeat in exon 1 of the *AR*
				Women	151	165	–	–	
				Men	65	67	–	–	
Colson (2005) (12)	Australia	Caucasian	Clinic	Women + men	263	277	227	50	Study population 2 from Colson (12). Other polymorphisms investigated: CAG repeat in exon 1 of the *AR*
				Women	222	238	–	–	
				Men	41	39	–	–	
Corominas (2009) (7)	Spain	Caucasian	NS	Women + men	210	210	86	102	'Any migraine' also contains 22 patients with hemiplegic migraine. Other polymorphisms investigated: rs2228480 (*ESR-1* 594 G > A), rs2077647 (*ESR-1*), and rs1801132 (*ESR-1* 325 C > G)
Joshi (2009) (8)	India	Indian	Clinic	Women + men	217	217	84	133	Other polymorphisms investigated: rs1801132 (*ESR-1* 325 C > G) and rs2234693 (*ESR-1* Pvu II C > T)
				Women	150	150	63	87	
				Men	67	67	21	46	
Total number of subjects					906	936	541	373	

MA: migraine with aura; MO: migraine without aura; NS: not specified; *ESR-1*: oestrogen receptor 1 gene; *MTHFR*: methylenetetrahydrofolate reductase gene; *PGR*: progesterone receptor gene.

Table 1B. Characteristics of the included studies according to the polymorphisms investigated – polymorphisms that have been investigated in single studies

Polymorphism(s)	Reference	Country	Ethnicity	Setting	Association
AR CAG repeat in exon 1	Colson (2005) (12)	Australia	Caucasian	Clinic	No
26 *ESR-1* polymorphisms (including rs1801132 and rs2228480)	Kaunisto (2006) (9)	Finland	Caucasian	Population and clinic	rs6557170, rs2347867, rs6557171, rs4870062, rs1801132 were nominally associated with MA, but did not remain significant after correction for multiple testing
FSHR rs6166	Oterino (2008) (11)	Spain	Caucasian	Clinic	Yes
ESR-2 rs4986938	Oterino (2008) (11)	Spain	Caucasian	Clinic	Yes
CYP19A1 rs10046	Oterino (2008) (11)	Spain	Caucasian	Clinic	Yes
NRIP1 rs2229741	Oterino (2008) (11)	Spain	Caucasian	Clinic	Yes
ESR-1 rs2077647	Corominas (2009) (7)	Spain	Caucasian	NS	No

AR: androgen receptor gene; *ESR-1*: oestrogen receptor 1 gene; *FSHR*: follicle stimulating hormone receptor gene; *ESR-2*: oestrogen receptor 2 gene; *CYP19A1*: cytochrome P450, family 19, subfamily A, polypeptide 1 gene; *NRIP1*: nuclear receptor interacting protein 1; MA: migraine with aura; NS: not specified.

Table 3 summarises for each of the studies the *P*-value for the HWE in the controls as well as ORs (95% CI) for the association between the polymorphisms and migraine assuming additive, dominant, and recessive genetic models.

Table 4 summarises the pooled effect estimates, measures for heterogeneity, and tests for publication bias for each of the polymorphisms.

Association between the ESR-1 594 G > A polymorphism and migraine

Among the five study populations from four studies investigating the association between the *ESR-1* 594 G > A polymorphism and migraine, there was a statistically significant positive association in two study populations (6) suggesting an increased risk for migraine among carriers of the A allele, which did not appear in the other studies (Table 3) (7,9,10).

The pooled effect estimates among all studies suggest that the A allele is associated with an increased risk for any migraine (additive mode: pooled OR 1.37; 95% CI 1.02–1.83; Table 4). The association appeared most pronounced for carriers of the GA/AA genotype (dominant mode: pooled OR 1.50; 95% CI 1.10–2.06). However, there was medium heterogeneity across all studies (dominant mode: $I^2 = 64.5\%$). Further, the increased risk for the GA/AA genotype appeared to be slightly higher among men (dominant mode: pooled OR 1.80; 95% CI 1.16–2.80) than among women (dominant mode: pooled OR 1.56; 95% CI 0.98–2.48), where it did not reach statistical significance. In addition, heterogeneity was medium among studies investigating women (dominant mode: $I^2 = 73.5\%$) and absent among studies investigating men. The results for MA and MO were very similar. Neither Begg's test nor Egger's test indicated publication bias for the dominant model.

Association between the ESR-1 325 C > G polymorphism and migraine

Among the six studies investigating the *ESR-1* 325 C > G polymorphism, two suggested an increased risk for migraine among carriers of the GG genotype (recessive mode), which appeared to be strongest among women (10,11), while the others did not find an altered risk (Table 3) (5,7–9).

The pooled effect estimates suggest that the G allele is associated with a slightly increased risk for having any migraine (additive mode: pooled OR 1.16; 95% CI 1.03–1.32; Table 4). The association was most pronounced for carriers of the GG genotype (recessive mode: pooled OR 1.40; 95% CI 0.93–2.11); however, this result did not reach statistical significance. Further, the effect estimates among studies in Caucasian populations were very similar to the overall result, which included a study in the Indian population. The association between the GG genotype and any migraine was stronger among women than men. Heterogeneity among the studies was low (recessive mode: $I^2 = 38.9\%$). The overall association was the same for MA (recessive mode: pooled OR 1.60; 95% CI 1.19–2.17) and MO (recessive mode: pooled OR 1.44; 95% CI 0.97–2.13). In addition, the pattern of a stronger association among women than men also occurred for MA and MO. Neither Begg's test nor Egger's test indicated publication bias when assuming a recessive model.

Table 2. Allele and genotype frequencies of the included studies according to the investigated polymorphisms

ESR-1 594 G > A polymorphism (rs2228480)								
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	G	A	GG	GA	AA
*Colson (2004) (6)	Women + men	Controls	224	323 (72.0)	125 (28.0)	112 (50.0)	99 (44.0)	13 (6.0)
		Any migraine	224	282 (63.0)	166 (37.0)	81 (36.0)	120 (54.0)	23 (10.0)
		MA	139	176 (63.0)	102 (37.0)	55 (40.0)	66 (47.0)	18 (13.0)
		MO	85	106 (62.0)	64 (38.0)	26 (31.0)	54 (64.0)	5 (6.0)
	Women	Controls	167	239 (72.0)	95 (28.0)	84 (50.0)	71 (43.0)	12 (7.0)
		Any migraine	167	213 (64.0)	121 (36.0)	63 (38.0)	87 (52.0)	17 (10.0)
		MA	103	135 (66.0)	71 (34.0)	44 (43.0)	47 (46.0)	12 (11.0)
		MO	64	78 (61.0)	50 (39.0)	19 (30.0)	40 (62.0)	5 (8.0)
	Men	Controls	57	84 (74.0)	30 (26.0)	28 (49.0)	28 (49.0)	1 (2.0)
		Any migraine	57	69 (61.0)	45 (39.0)	18 (32.0)	33 (58.0)	6 (10.0)
		MA	36	41 (57.0)	31 (43.0)	11 (31.0)	19 (53.0)	6 (16.0)
		MO	21	28 (68.0)	14 (32.0)	7 (33.0)	14 (67.0)	0 (0.0)
*Colson (2004) (6)	Women + men	Controls	260	397 (76.0)	123 (24.0)	152 (58.0)	93 (36.0)	15 (6.0)
		Any migraine	260	331 (64.0)	189 (36.0)	103 (40.0)	125 (48.0)	32 (12.0)
		MA	221	274 (62.0)	168 (38.0)	82 (37.0)	110 (50.0)	29 (13.0)
		MO	39	57 (73.0)	21 (27.0)	21 (54.0)	15 (38.0)	3 (8.0)
	Women	Controls	224	346 (77.0)	102 (23.0)	132 (59.0)	82 (37.0)	10 (4.0)
		Any migraine	224	282 (63.0)	166 (37.0)	88 (39.0)	106 (47.0)	30 (14.0)
		MA	191	235 (62.0)	147 (38.0)	71 (37.0)	93 (49.0)	27 (14.0)
		MO	33	47 (71.0)	19 (29.0)	17 (52.0)	13 (39.0)	3 (9.0)
	Men	Controls	36	51 (71.0)	21 (29.0)	20 (55.0)	11 (31.0)	5 (14.0)
		Any migraine	36	49 (68.0)	23 (32.0)	15 (42.0)	19 (53.0)	2 (5.0)
		MA	30	39 (65.0)	21 (35.0)	11 (37.0)	17 (56.0)	2 (7.0)
		MO	6	10 (83.0)	2 (17.0)	4 (67.0)	2 (33.0)	0 (0.0)
Oterino (2006) (10)	Women + men	Controls	232	380 (81.9)	84 (18.1)	161 (69.4)	58 (25.0)	13 (5.6)
		Any migraine	367	591 (80.5)	143 (19.5)	240 (65.4)	111 (30.2)	16 (4.4)
		MA	197	317 (80.5)	77 (19.5)	128 (64.9)	61 (31.0)	8 (4.1)
		MO	170	274 (80.6)	66 (19.4)	112 (65.9)	50 (29.4)	8 (4.7)
	Women	Controls	142	232 (81.8)	52 (18.2)	93 (65.5)	38 (26.8)	11 (7.7)
		Any migraine	286	461 (80.6)	111 (19.4)	187 (65.5)	87 (30.3)	12 (4.2)
		MA	155	248 (80.0)	62 (20.0)	99 (63.8)	50 (32.3)	6 (3.9)
		MO	131	213 (81.3)	49 (18.7)	88 (67.2)	37 (28.2)	6 (4.6)
	Men	Controls	90	156 (86.7)	24 (13.3)	68 (75.6)	20 (20.2)	2 (2.2)
		Any migraine	81	130 (80.2)	32 (19.8)	53 (65.4)	24 (29.7)	4 (4.9)
		MA	42	69 (82.1)	15 (17.9)	29 (69.0)	11 (26.2)	2 (4.8)
		MO	39	61 (78.2)	17 (21.8)	24 (61.5)	13 (33.4)	2 (5.1)
Kaunisto (2006) (9)	Women + men	Controls	900	1458 (81.0)	342 (19.0)	594 (66.0)	270 (30.0)	36 (4.0)
		MA	898	1428 (80.0)	368 (20.0)	566 (63.0)	296 (33.0)	36 (4.0)
Corominas (2009) (7)	Women + men	Controls	210	361 (86.0)	59 (14.0)	157 (74.8)	47 (22.4)	6 (2.9)
		Any migraine	210	360 (85.7)	60 (14.3)	154 (73.3)	52 (24.8)	4 (1.9)
		MA	86	150 (87.2)	22 (12.8)	65 (75.6)	20 (23.3)	1 (1.2)
		MO	102	171 (83.8)	33 (16.2)	72 (70.6)	27 (26.5)	3 (2.9)

(continued)

Table 2. Continued

ESR-1 325 C > G polymorphism (rs1801132)								
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	C	G	CC	CG	GG
Colson (2006) (5)	Women + men	Controls	249	396 (79.0)	102 (21.0)	160 (64.0)	76 (31.0)	13 (5.0)
		Any migraine	231	356 (77.0)	106 (23.0)	133 (58.0)	90 (39.0)	8 (3.0)
		MA	141	213 (76.0)	69 (24.0)	77 (55.0)	59 (42.0)	5 (3.0)
		MO	75	120 (80.0)	30 (20.0)	47 (62.0)	26 (35.0)	2 (3.0)
	Women	Controls	189	302 (80.0)	76 (20.0)	122 (64.0)	58 (31.0)	9 (5.0)
		Any migraine	167	254 (76.0)	80 (24.0)	94 (56.0)	66 (40.0)	7 (4.0)
	Men	Controls	60	94 (78.0)	26 (22.0)	38 (63.0)	18 (30.0)	4 (7.0)
		Any migraine	64	102 (80.0)	26 (20.0)	39 (61.0)	24 (37.0)	1 (2.0)
Oterino (2006) (10)	Women + men	Controls	232	377 (81.3)	87 (18.8)	159 (68.5)	59 (25.5)	14 (6.0)
		Any migraine	367	568 (77.4)	166 (22.6)	238 (64.9)	92 (25.0)	37 (10.1)
		MA	197	304 (77.2)	90 (22.8)	127 (64.5)	50 (25.4)	20 (10.1)
		MO	170	264 (77.6)	76 (22.4)	111 (65.3)	42 (24.7)	17 (10.0)
	Women	Controls	142	237 (83.5)	47 (16.5)	101 (71.1)	35 (24.7)	6 (4.2)
		Any migraine	286	432 (75.5)	140 (24.5)	179 (62.6)	74 (25.9)	33 (11.5)
		MA	155	233 (75.2)	77 (24.8)	96 (61.9)	41 (26.5)	18 (11.6)
		MO	131	199 (76.0)	63 (24.0)	83 (63.4)	33 (25.2)	15 (11.4)
	Men	Controls	90	140 (77.8)	40 (22.2)	58 (64.4)	24 (26.7)	8 (8.9)
		Any migraine	81	136 (84.0)	26 (16.0)	59 (72.9)	18 (22.2)	4 (4.9)
		MA	42	71 (84.5)	13 (15.5)	31 (73.8)	9 (21.4)	2 (4.8)
		MO	39	65 (83.3)	13 (16.7)	28 (71.8)	9 (23.1)	2 (5.1)
Kaunisto (2006) (9)	Women + men	Controls	888	1363 (77.0)	413 (23.0)	513 (58.0)	337 (38.0)	38 (4.0)
		MA	896	1328 (74.0)	464 (26.0)	499 (57.0)	330 (37.0)	67 (7.0)
Oterino (2008) (11)	Women + men	Controls	372	615 (82.7)	129 (17.3)	257 (69.1)	101 (27.2)	14 (3.8)
		Any migraine	356	557 (78.2)	155 (21.8)	230 (64.6)	97 (27.2)	29 (8.1)
		MA	198	308 (77.8)	88 (22.2)	126 (63.6)	56 (28.3)	16 (8.1)
		MO	158	249 (78.8)	67 (21.2)	104 (65.8)	41 (25.9)	13 (8.2)
	Women	Controls	263	438 (83.3)	88 (16.7)	185 (70.3)	68 (25.9)	10 (3.8)
		Any migraine	269	411 (76.4)	127 (23.6)	167 (62.1)	77 (28.6)	25 (9.3)
		MA	152	230 (75.7)	74 (24.3)	92 (60.5)	46 (30.3)	14 (9.2)
		MO	117	181 (77.4)	53 (22.6)	75 (64.1)	31 (26.5)	11 (9.4)
	Men	Controls	109	177 (81.2)	41 (18.8)	72 (66.0)	33 (30.3)	4 (3.7)
		Any migraine	87	146 (83.9)	28 (16.1)	63 (72.4)	20 (23.0)	4 (4.6)
		MA	46	78 (84.8)	14 (15.2)	34 (73.9)	10 (21.7)	2 (4.3)
		MO	41	68 (82.9)	14 (17.1)	29 (70.7)	10 (24.4)	2 (4.9)
Corominas (2009) (7)	Women + men	Controls	210	339 (80.7)	81 (19.3)	136 (64.8)	67 (31.9)	7 (3.3)
		Any migraine	210	338 (80.5)	82 (19.5)	140 (66.7)	58 (27.6)	12 (5.7)
		MA	86	135 (78.5)	37 (21.5)	55 (64.0)	25 (29.1)	6 (7.0)
		MO	102	169 (82.8)	35 (17.2)	72 (70.6)	25 (24.5)	5 (4.9)
Joshi (2009) (8)	Women + men	Controls	217	272 (62.7)	162 (37.3)	81 (37.3)	110 (50.7)	26 (12.0)
		Any migraine	217	265 (61.1)	169 (38.9)	75 (34.6)	115 (53.0)	27 (12.4)
		MA	84	106 (63.1)	62 (36.9)	32 (38.1)	42 (50.0)	10 (11.9)
		MO	133	159 (59.8)	107 (40.8)	43 (32.3)	73 (54.9)	17 (12.8)
	Women	Controls	150	185 (61.7)	115 (38.3)	53 (35.3)	79 (52.7)	18 (12.0)
		Any migraine	150	185 (61.7)	115 (38.3)	55 (36.7)	75 (50.0)	20 (13.3)

(continued)

Table 2. Continued

ESR-1 325 C > G polymorphism (rs1801132)								
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	C	G	CC	CG	GG
		MA	63	82 (65.1)	44 (34.9)	26 (41.3)	30 (47.6)	7 (11.6)
		MO	87	103 (59.2)	71 (40.8)	29 (33.3)	45 (51.7)	13 (14.9)
	Men	Controls	67	87 (64.9)	47 (35.1)	28 (41.8)	31 (46.3)	8 (11.9)
		Any migraine	67	80 (59.7)	54 (40.3)	20 (29.9)	40 (59.7)	7 (10.4)
		MA	21	24 (57.1)	18 (42.9)	6 (28.6)	12 (57.1)	3 (14.3)
		MO	46	56 (60.9)	36 (39.1)	14 (30.4)	28 (60.9)	4 (8.7)
ESR-1 Pvu II C > T (rs2234693)								
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	C	T	CC	CT	TT
Colson (2006) (5)	Women + men	Controls	202	189 (47.0)	215 (53.0)	46 (23.0)	97 (48.0)	59 (29.0)
		Any migraine	231	232 (50.0)	230 (50.0)	55 (24.0)	122 (53.0)	54 (23.0)
		MA	145	142 (49.0)	148 (51.0)	29 (20.0)	84 (58.0)	32 (22.0)
		MO	73	77 (53.0)	69 (47.0)	22 (30.0)	33 (45.0)	18 (25.0)
	Women	Controls	140	138 (49.0)	142 (51.0)	34 (24.0)	70 (50.0)	36 (26.0)
		Any migraine	167	167 (50.0)	167 (50.0)	38 (23.0)	91 (54.0)	38 (23.0)
	Men	Controls	62	51 (41.0)	73 (59.0)	12 (19.0)	27 (44.0)	23 (37.0)
		Any migraine	64	65 (51.0)	63 (49.0)	17 (27.0)	31 (48.0)	16 (25.0)
Joshi (2009) (8)	Women + men	Controls	217	287 (66.1)	147 (33.9)	88 (40.6)	111 (51.2)	18 (8.3)
		Any migraine	217	230 (53.0)	204 (47.0)	47 (21.7)	136 (62.7)	34 (15.7)
		MA	84	86 (51.2)	82 (48.8)	14 (16.7)	58 (69.0)	12 (14.3)
		MO	133	144 (54.1)	122 (45.9)	33 (24.8)	78 (58.6)	22 (16.5)
	Women	Controls	150	201 (67.0)	99 (33.0)	61 (40.7)	79 (52.7)	10 (6.7)
		Any migraine	150	161 (53.7)	139 (46.3)	34 (36.7)	93 (50.0)	23 (13.3)
		MA	63	65 (51.6)	61 (58.4)	10 (15.9)	45 (71.4)	8 (12.7)
		MO	87	96 (55.2)	78 (44.8)	24 (27.6)	48 (55.2)	15 (17.2)
	Men	Controls	67	86 (64.2)	48 (35.8)	27 (40.3)	32 (47.8)	8 (11.9)
		Any migraine	67	69 (51.5)	65 (48.5)	13 (19.4)	43 (64.2)	11 (16.4)
		MA	21	21 (50.0)	21 (50.0)	4 (19.0)	13 (61.9)	4 (19.0)
		MO	46	48 (52.2)	44 (47.8)	9 (19.6)	30 (65.2)	7 (15.2)
PGR PROGINS insert								
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	1	2	11	12	22
†Colson (2005) (12)	Women + men	Controls	216	395 (91.0)	37 (9.0)	182 (84.0)	31 (15.0)	3 (1.0)
		Any migraine	232	401 (86.0)	63 (14.0)	173 (75.0)	55 (23.0)	4 (2.0)
		MA	144	253 (88.0)	35 (12.0)	113 (78.0)	27 (19.0)	4 (3.0)
		MO	88	148 (84.0)	28 (16.0)	60 (68.0)	28 (32.0)	0 (0.0)
	Women	Controls	151	287 (95.0)	15 (5.0)	138 (91.0)	11 (7.0)	2 (2.0)
		Any migraine	165	293 (89.0)	37 (11.0)	130 (79.0)	33 (20.0)	2 (1.0)
	Men	Controls	65	108 (83.0)	22 (17.0)	44 (68.0)	20 (31.0)	1 (1.0)
		Any migraine	67	108 (81.0)	26 (19.0)	43 (64.0)	22 (33.0)	2 (3.0)

(continued)

Table 2. Continued

				PGR PROGINS insert				
				Allele frequencies, *n* (%)		Genotype frequencies, *n* (%)		
Reference	Population	Disease status	Study size	1	2	11	12	22
†Colson (2005) (12)	Women + men	Controls	263	488 (93.0)	38 (7.0)	228 (87.0)	32 (12.0)	3 (1.0)
		Any migraine	277	484 (87.0)	70 (13.0)	215(78.0)	54 (19.0)	8 (3.0)
		MA	227	397 (87.0)	57 (13.0)	176 (77.0)	45 (20.0)	6 (3.0)
		MO	50	87 (87.0)	13 (13.0)	39 (78.0)	9 (18.0)	2 (4.0)
	Women	Controls	222	412 (93.0)	32 (7.0)	193 (87.0)	26 (12.0)	3 (1.0)
		Any migraine	238	422 (89.0)	54 (11.0)	188 (79.0)	46 (19.0)	4 (2.0)
	Men	Controls	41	76 (93.0)	6 (7.0)	35 (85.0)	6 (15.0)	0 (0.0)
		Any migraine	39	62 (79.0)	16 (21.0)	27 (69.0)	8 (20.0)	4 (11.0)
Corominas (2009) (7)	Women + men	Controls	210	344 (81.9)	76 (18.1)	142 (67.6)	60 (28.6)	8 (3.8)
		Any migraine	210	346 (82.4)	74 (17.6)	142 (67.6)	62 (29.5)	6 (2.9)
		MA	86	139 (80.8)	33 (19.2)	56 (65.1)	27 (31.4)	3 (3.5)
		MO	102	172 (84.3)	32 (15.7)	72 (70.6)	28 (27.5)	2 (2.0)
Joshi (2009) (8)	Women + men	Controls	217	392 (90.3)	42 (9.7)	175 (80.6)	42 (19.4)	0 (0.0)
		Any migraine	217	418 (96.3)	16 (3.7)	201 (92.6)	16 (7.4)	0 (0.0)
		MA	84	161 (95.8)	7 (4.2)	77 (91.8)	7 (8.2)	0 (0.0)
		MO	133	257 (96.6)	9 (3.4)	124 (93.2)	9 (6.8)	0 (0.0)
	Women	Controls	150	267 (89.0)	33 (11.0)	117 (78.0)	33 (22.0)	0 (0.0)
		Any migraine	150	285 (95.0)	15 (5.0)	135 (90.0)	15 (10.0)	0 (0.0)
		MA	63	119 (94.4)	7 (5.6)	56 (88.9)	7 (11.1)	0 (0.0)
		MO	87	166 (95.4)	8 (4.6)	79 (90.8)	8 (9.2)	0 (0.0)
	Men	Controls	67	125 (93.3)	9 (6.7)	58 (86.6)	9 (13.4)	0 (0.0)
		Any migraine	67	133 (99.3)	1 (0.7)	66 (98.5)	1 (1.5)	0 (0.0)
		MA	21	42 (100.0)	0 (0.0)	21 (100.0)	0 (0.0)	0 (0.0)
		MO	46	91 (98.9)	1 (1.1)	45 (97.8)	1 (2.2)	0 (0.0)

*Two study populations from Colson et al. (2004) (6).
†Two study populations from Colson et al. (2005) (12).
MA, migraine with aura; MO, migraine without aura; *ESR-1*, oestrogen receptor 1 gene; *PGR*, progesterone receptor gene.

Association between the ESR-1 Pvu II C > T polymorphism and migraine

Among the two studies investigating the *ESR-1* Pvu II C > T polymorphism, one found an increased risk for migraine among carriers of the T allele (8), while the other did not (Table 3) (5).

The pooled effect estimates of the two studies neither suggest an association for any of the genotypes with any migraine, MA or MO nor a difference between women and men when looking at any migraine. One study provided gender specific effect estimates for MA and MO, which suggested a higher risk among women than men (8). Heterogeneity between the two studies was high. This is most likely due to the low number of studies and remaining uncertainties which may include genotypic ethnic differences. Formal investigation using Begg's test did not indicate publication bias.

Association between the PGR PROGINS insert polymorphism and migraine

Among the four study populations investigating the *PGR* PROGINS insert polymorphism, two found an increased risk among carriers of the '2' allele (*Alu* insert) (12), one found a protective association (8), and one did not find an association (Table 3) (7).

The pooled effect estimates among all studies do not suggest an association between any of the genotypes and any migraine (additive mode: pooled OR 1.02; 95% CI 0.55–1.87; Table 4). This finding did not differ between MA (additive mode: pooled OR 1.11; 95% CI 0.68–1.81) and MO (additive mode: pooled OR 1.01; 95% CI 0.48–2.13). However, further analyses

Table 3. Hardy–Weinberg Equilibrium and odds ratios (95% CI) for additive, dominant, and recessive genetic models according to the investigated polymorphisms

Reference	Population	Disease status	Study size	HWE	Additive		Dominant		Recessive	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
					ESR-1 594 G > A (rs2228480)					
*Colson (2004) (6)	Women + men	Controls	224	0.18	Referent		Referent		Referent	
		Any migraine	224	–	1.62 (1.19–2.19)	0.002	1.77 (1.21–2.58)	0.003	1.86 (0.92–3.77)	0.86
		MA	139	–	1.54 (1.10–2.16)	0.01	1.53 (0.99–2.35)	0.05	2.41 (1.14–5.10)	0.02
		MO	85	–	1.73 (1.13–2.63)	0.01	2.27 (1.34–3.86)	0.003	1.01 (0.35–2.94)	0.98
	Women	Controls	167	0.71	Referent		Referent		Referent	
		Any migraine	167	–	1.48 (1.05–2.09)	0.03	1.67 (1.08–2.58)	0.02	1.46 (0.68–3.17)	0.33
		MA	103	–	1.34 (0.91–1.95)	0.14	1.36 (0.83–2.23)	0.23	1.70 (0.74–3.95)	0.21
		MO	64	–	1.74 (1.09–2.77)	0.02	2.40 (1.29–4.44)	0.005	1.10 (0.37–3.24)	0.87
	Men	Controls	57	0.08	Referent		Referent		Referent	
		Any migraine	57	–	2.20 (1.14–4.25)	0.02	2.09 (0.98–4.49)	0.06	6.59 (0.77–56.55)	0.09
		MA	36	–	2.52 (1.22–5.24)	0.01	2.19 (0.91–5.28)	0.08	11.20 (1.29–97.37)	0.03
		MO	21	–	1.69 (0.64–4.48)	0.29	1.93 (0.68–5.49)	0.22	–	–
*Colson (2004) (6)	Women + men	Controls	260	0.87	Referent		Referent		Referent	
		Any migraine	260	–	1.86 (1.41–2.46)	<0.0001	2.15 (1.51–3.05)	< 0.0001	2.29 (1.21–4.34)	0.01
		MA	221	–	2.01 (1.51–2.69)	< 0.0001	2.39 (1.65–3.45)	< 0.0001	2.47 (1.29–4.73)	0.007
		MO	39	–	1.19 (0.69–2.03)	0.53	1.21 (0.61–2.37)	0.59	1.36 (0.38–4.94)	0.64
	Women	Controls	224	0.70	Referent		Referent		Referent	
		Any migraine	224	–	2.03 (1.50–2.75)	< 0.0001	2.22 (1.52–3.24)	< 0.0001	3.31 (1.58–6.95)	0.002
		MA	191	–	2.18 (1.59–2.99)	< 0.0001	2.43 (1.63–3.60)	< 0.0001	3.52 (1.66–7.49)	0.001
		MO	33	–	1.39 (0.77–2.49)	0.28	1.35 (0.65–2.81)	0.42	2.14 (0.56–8.22)	0.27
	Men	Controls	36	0.12	Referent		Referent		Referent	
		Any migraine	36	–	1.14 (0.56–2.30)	0.72	1.75 (0.69–4.45)	0.24	0.37 (0.07–2.02)	0.25
		MA	30	–	1.30 (0.63–2.70)	0.48	2.16 (0.80–5.82)	0.13	0.44 (0.08–2.47)	0.35
		MO	6	–	0.55 (0.12–2.42)	0.43	0.63 (0.10–3.86)	0.61	–	–
Oterino (2006) (10)	Women + men	Controls	232	0.03	Referent		Referent		Referent	
		Any migraine	367	–	1.09 (0.82–1.45)	0.57	1.20 (0.84–1.71)	0.31	0.77 (0.36–1.63)	0.49
		MA	197	–	1.09 (0.79–1.52)	0.61	1.22 (0.82–1.83)	0.33	0.71 (0.29–1.76)	0.46

(continued)

Table 3. Continued

Reference	Population	Disease status	Study size	HWE	Additive OR (95% CI)	Additive *P*-value	Dominant OR (95% CI)	Dominant *P*-value	Recessive OR (95% CI)	Recessive *P*-value
		MO	170	–	1.08 (0.77–1.52)	0.66	1.17 (0.77–1.79)	0.46	0.83 (0.34–2.05)	0.69
	Women	Controls	142	0.02	Referent		Referent		Referent	
		Any migraine	286	–	0.91 (0.65–1.27)	0.57	1.01 (0.66–1.53)	0.98	0.52 (0.22–1.21)	0.13
		MA	155	–	0.94 (0.64–1.37)	0.75	1.07 (0.67–1.73)	0.77	0.48 (0.17–1.33)	0.16
		MO	131	–	0.88 (0.59–1.30)	0.51	0.93 (0.56–1.53)	0.77	0.57 (0.21–1.59)	0.28
	Men	Controls	90	0.64	Referent		Referent		Referent	
		Any migraine	81	–	1.56 (0.89–2.76)	0.12	1.63 (0.84–3.17)	0.15	2.29 (0.41–12.82)	0.35
		MA	42	–	1.38 (0.70–2.74)	0.35	1.39 (0.62–3.12)	0.43	2.20 (0.30–16.18)	0.44
		MO	39	–	1.78 (0.90–3.53)	0.10	1.93 (0.86–4.32)	0.11	2.38 (0.32–17.52)	0.40
Kaunisto (2006) (9)	Women + men	Controls	900	0.45	Referent		Referent		Referent	
		MA	898	–	1.10 (0.93–1.30)	0.26	1.14 (0.94–1.29)	0.19	1.00 (0.63–1.61)	0.99
Corominas (2009) (7)	Women + men	Controls	210	0.26	Referent		Referent		Referent	
		Any migraine	210	–	1.02 (0.70–1.49)	0.92	1.08 (0.70–1.67)	0.74	0.66 (0.18–2.37)	0.52
		MA	86	–	0.90 (0.54–1.51)	0.69	0.96 (0.54–1.71)	0.88	0.40 (0.05–3.37)	0.34
		MO	102	–	1.17 (0.75–1.84)	0.49	1.23 (0.73–2.09)	0.43	1.03 (0.25–4.21)	0.97
					ESR-1 325 C > G (rs1801132)					
Colson (2006) (5)	Women + men	Controls	249	0.34	Referent		Referent		Referent	
		Any migraine	231	–	1.16 (0.85–1.58)	0.35	1.33 (0.92–1.91)	0.13	0.65 (0.27–1.60)	0.35
		MA	141	–	1.26 (0.89–1.79)	0.19	1.49 (0.98–2.28)	0.06	0.67 (0.23–1.91)	0.45
		MO	75	–	0.97 (0.62–1.52)	0.90	1.07 (0.63–1.83)	0.80	0.50 (0.11–2.26)	0.37
	Women	Controls	189	0.50	Referent		Referent		Referent	
		Any migraine	167	–	1.26 (0.88–1.80)	0.21	1.41 (0.92–2.17)	0.11	0.88 (0.32–2.41)	0.80
	Men	Controls	60	0.45	Referent		Referent		Referent	
		Any migraine	64	–	0.92 (0.50–1.71)	0.79	1.11 (0.54–2.29)	0.78	0.22 (0.02–2.05)	0.18
Oterino (2006) (10)	Women + men	Controls	232	0.02	Referent		Referent		Referent	
		Any migraine	367	–	1.21 (0.93–1.57)	0.15	1.18 (0.83–1.68)	0.35	1.75 (0.92–3.30)	0.09
		MA	197	–	1.23 (0.91–1.66)	0.18	1.20 (0.80–1.80)	0.37	1.76 (0.86–3.58)	0.12
		MO	170	–	1.20 (0.88–1.64)	0.26	1.16 (0.76–1.76)	0.49	1.73 (0.83–3.62)	0.14

(continued)

Table 3. Continued

Reference	Population	Disease status	Study size	HWE	Additive		Dominant		Recessive	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
	Women	Controls	142	0.22	Referent		Referent		Referent	
		Any migraine	286	–	1.49 (1.07–2.07)	0.02	1.47 (0.95–2.28)	0.08	2.96 (1.21–7.23)	0.02
		MA	155	–	1.52 (1.05–2.21)	0.03	1.51 (0.93–2.46)	0.09	2.98 (1.15–7.73)	0.02
		MO	131	–	1.47 (1.00–2.16)	0.05	1.43 (0.86–2.37)	0.17	2.93 (1.10–7.80)	0.03
	Men	Controls	90	0.04	Referent		Referent		Referent	
		Any migraine	81	–	0.72 (0.43–1.18)	0.19	0.68 (0.35–1.30)	0.24	0.53 (0.15–1.84)	0.32
		MA	42	–	0.69 (0.37–1.30)	0.25	0.64 (0.29–1.45)	0.29	0.51 (0.10–2.53)	0.41
		MO	39	–	0.74 (0.40–1.40)	0.36	0.71 (0.31–1.62)	0.42	0.55 (0.11–2.74)	0.47
Kaunisto (2006) (9)	Women + men	Controls	888	0.07	Referent		Referent		Referent	
		MA	896	–	1.16 (0.99–1.35)	0.07	1.09 (0.90–1.31)	0.38	1.81 (1.20–2.72)	0.005
Oterino (2008) (11)	Women + men	Controls	372	0.27	Referent		Referent		Referent	
		Any migraine	356	–	1.28 (1.01–1.64)	0.05	1.22 (0.90–1.67)	0.20	2.27 (1.18–4.37)	0.01
		MA	198	–	1.32 (0.99–1.77)	0.06	1.28 (0.89–1.84)	0.19	2.25 (1.07–4.71)	0.03
		MO	158	–	1.25 (0.92–1.71)	0.16	1.16 (0.78–1.72)	0.46	2.29 (1.05–5.00)	0.04
	Women	Controls	263	0.27	Referent		Referent		Referent	
		Any migraine	269	–	1.46 (1.09–1.94)	0.01	1.45 (1.01–2.08)	0.04	2.59 (1.22–5.51)	0.01
		MA	152	–	1.52 (1.09–2.12)	0.01	1.55 (1.02–2.35)	0.04	2.57 (1.11–5.93)	0.03
		MO	117	–	1.39 (0.97–2.00)	0.07	1.33 (0.84–2.11)	0.23	2.62 (1.08–6.36)	0.03
	Men	Controls	109	1	Referent		Referent		Referent	
		Any migraine	87	–	0.84 (0.50–1.40)	0.50	0.74 (0.40–1.37)	0.34	1.27 (0.31–5.21)	0.74
		MA	46	–	0.78 (0.41–1.50)	0.46	0.69 (0.32–1.48)	0.34	1.19 (0.21–6.75)	0.84
		MO	41	–	0.89 (0.46–1.72)	0.73	0.81 (0.37–1.76)	0.59	1.35 (0.24–7.65)	0.74
Corominas (2009) (7)	Women + men	Controls	210	0.83	Referent		Referent		Referent	
		Any migraine	210	–	1.02 (0.73–1.42)	0.93	0.92 (0.61–1.38)	0.68	1.76 (0.68–4.56)	0.25
		MA	86	–	1.14 (0.74–1.76)	0.54	1.04 (0.61–1.75)	0.89	2.18 (0.71–6.67)	0.17
		MO	102	–	0.87 (0.56–1.34)	0.53	0.77 (0.46–1.28)	0.31	1.50 (0.46–4.83)	0.50
Joshi (2009) (8)	Women + men	Controls	217	0.25	Referent		Referent		Referent	
		Any migraine	217	–	1.08 (0.81–1.44)	0.61	1.13 (0.76–1.67)	0.55	1.04 (0.59–1.86)	0.88

(continued)

Table 3. Continued

Reference	Population	Disease status	Study size	HWE	Additive OR (95% CI)	Additive *P*-value	Dominant OR (95% CI)	Dominant *P*-value	Recessive OR (95% CI)	Recessive *P*-value
		MA	84	–	0.98 (0.67–1.44)	0.92	0.97 (0.58–1.63)	0.90	0.99 (0.46–2.16)	0.99
		MO	133	–	1.15 (0.82–1.60)	0.42	1.25 (0.79–1.97)	0.34	1.08 (0.56–2.07)	0.82
	Women	Controls	150	0.23	Referent		Referent		Referent	
		Any migraine	150	–	1.00 (0.71–1.41)	1	0.94 (0.59–1.51)	0.81	1.13 (0.57–2.23)	0.73
		MA	63	–	0.85 (0.54–1.34)	0.49	0.78 (0.43–1.42)	0.41	0.92 (0.36–2.32)	0.85
		MO	87	–	1.12 (0.75–1.68)	0.58	1.09 (0.63–1.91)	0.76	1.29 (0.60–2.78)	0.52
	Men	Controls	67	1	Referent		Referent		Referent	
		Any migraine	67	–	1.29 (0.76–2.20)	0.35	1.69 (0.83–3.45)	0.15	0.86 (0.29–2.52)	0.78
		MA	21	–	1.42 (0.68–2.94)	0.35	1.80 (0.62–5.20)	0.28	1.23 (0.30–5.13)	0.78
		MO	46	–	1.22 (0.68–2.20)	0.51	1.64 (0.74–3.63)	0.22	0.70 (0.20–2.49)	0.58
					ESR-1 Pvu II C > T (rs2234693)					
Colson (2006) (5)	Women + men	Controls	202	0.67	Referent		Referent		Referent	
		Any migraine	231	–	0.87 (0.66–1.14)	0.31	0.94 (0.60–1.48)	0.80	0.74 (0.48–1.14)	0.17
		MA	145	–	0.91 (0.67–1.24)	0.56	1.18 (0.70–1.99)	0.54	0.69 (0.42–1.13)	0.14
		MO	73	–	0.80 (0.55–1.16)	0.23	0.68 (0.38–1.24)	0.21	0.79 (0.43–1.46)	0.46
	Women	Controls	140	1	Referent		Referent		Referent	
		Any migraine	167	–	0.97 (0.70–1.34)	0.86	1.09 (0.64–1.85)	0.75	0.85 (0.50–1.44)	0.55
	Men	Controls	62	0.44	Referent		Referent		Referent	
		Any migraine	64	–	0.69 (0.43–1.13)	0.14	0.66 (0.29–1.54)	0.34	0.57 (0.26–1.22)	0.14
Joshi (2009) (8)	Women + men	Controls	217	0.049	Referent		Referent		Referent	
		Any migraine	217	–	2.00 (1.45–2.74)	<0.0001	2.47 (1.62–3.76)	< 0.0001	2.05 (1.12–3.76)	0.02
		MA	84	–	2.23 (1.45–3.43)	0.0002	3.41 (1.81–6.43)	0.0002	1.84 (0.85–4.02)	0.12
		MO	133	–	1.82 (1.29–2.59)	0.0008	2.07 (1.28–3.33)	0.003	2.19 (1.13–4.26)	0.02
	Women	Controls	150	0.03	Referent		Referent		Referent	
		Any migraine	150	–	2.06 (1.40–3.03)	0.0003	2.34 (1.42–3.86)	0.0009	2.53 (1.16–5.53)	0.02
		MA	63	–	2.47 (1.45–4.19)	0.0009	3.63 (1.72–7.69)	0.0008	2.04 (0.76–5.43)	0.16
		MO	87	–	1.82 (1.19–2.80)	0.006	1.80 (1.02–3.19)	0.04	2.92 (1.25–6.82)	0.01
	Men	Controls	67	1	Referent		Referent		Referent	
		Any migraine	67	–	1.88 (1.08–3.26)	0.03	2.80 (1.29–6.10)	0.009	1.45 (0.54–3.87)	0.46

(continued)

Table 3. Continued

Reference	Population	Disease status	Study size	HWE	Additive OR (95% CI)	Additive *P*-value	Dominant OR (95% CI)	Dominant *P*-value	Recessive OR (95% CI)	Recessive *P*-value
		MA	21	–	1.90 (0.90–4.03)	0.09	2.87 (0.87–9.46)	0.08	1.74 (0.47–6.47)	0.41
		MO	46	–	1.80 (0.99–3.29)	0.06	2.78 (1.16–6.67)	0.02	1.32 (0.44–3.95)	0.61
					PGR PROGINS insert					
†Colson	Women + men	Controls	216	0.2	Referent		Referent		Referent	
(2005) (12)		Any migraine	232	–	1.66 (1.08–2.54)	0.02	1.83 (1.14–2.92)	0.01	1.25 (0.28–5.63)	0.78
		MA	144	–	1.42 (0.89–2.27)	0.14	1.47 (0.86–2.52)	0.16	2.03 (0.45–9.20)	0.36
		MO	88	–	2.06 (1.20–3.54)	0.009	2.50 (1.40–4.46)	0.002	–	–
	Women	Controls	151	0.04	Referent		Referent		Referent	
		Any migraine	165	–	2.30 (1.25–4.26)	0.008	2.86 (1.45–5.64)	0.003	0.91 (0.13–6.57)	0.93
	Men	Controls	65	0.67	Referent		Referent		Referent	
		Any migraine	67	–	1.20 (0.62–2.30)	0.59	1.17 (0.57–2.40)	0.67	1.97 (0.17–22.26)	0.58
†Colson	Women + men	Controls	263	0.14	Referent		Referent		Referent	
(2005) (12)		Any migraine	277	–	1.75 (1.18–2.62)	0.006	1.88 (1.19–2.96)	0.007	2.58 (0.68–9.81)	0.17
		MA	227	–	1.75 (1.15–2.66)	0.008	1.89 (1.18–3.03)	0.009	2.35 (0.58–9.52)	0.23
		MO	50	–	1.78 (0.95–3.34)	0.07	1.84 (0.86–3.92)	0.12	3.61 (0.59–22.19)	0.17
	Women	Controls	222	0.09	Referent		Referent		Referent	
		Any migraine	238	–	1.60 (1.02–2.49)	0.04	1.77 (1.07–2.92)	0.03	1.25 (0.28–5.64)	0.77
	Men	Controls	41	1	Referent		Referent		Referent	
		Any migraine	39	–	2.66 (1.04–6.82)	0.04	2.59 (0.86–7.80)	0.09	–	–
Corominas	Women + men	Controls	210	0.64	Referent		Referent		Referent	
(2009) (7)		Any migraine	210	–	0.97 (0.68–1.38)	0.86	1.00 (0.66–1.51)	1	0.74 (0.25–2.18)	0.59
		MA	86	–	1.07 (0.69–1.68)	0.76	1.12 (0.66–1.90)	0.68	0.91 (0.24–3.53)	0.89
		MO	102	–	0.84 (0.54–1.32)	0.46	0.87 (0.52–1.46)	0.60	0.51 (0.11–2.42)	0.39
Joshi (2009) (8)	Women + men	Controls	217	0.23	Referent		Referent		Referent	
		Any migraine	217	–	0.33 (0.18–0.61)	0.0004	0.33 (0.18–0.61)	0.0004	–	–
		MA	84	–	0.38 (0.16–0.88)	0.02	0.38 (0.16–0.88)	0.02	–	–
		MO	133	–	0.30 (0.14–0.64)	0.002	0.30 (0.14–0.64)	0.002	–	–
	Women	Controls	150	0.22	Referent		Referent		Referent	

(continued)

Table 3. Continued

Reference	Population	Disease status	Study size	HWE	Additive		Dominant		Recessive	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
		Any migraine	150	–	0.39 (0.20–0.76)	0.006	0.39 (0.20–0.76)	0.006	–	–
		MA	63	–	0.44 (0.19–1.06)	0.07	0.44 (0.19–1.06)	0.07	–	–
		MO	87	–	0.36 (0.16–0.82)	0.01	0.36 (0.16–0.82)	0.01	–	–
	Men	Controls	67	–	Referent		Referent		Referent	
		Any migraine	67	–	0.10 (0.01–0.79)	0.03	0.10 (0.01–0.79)	0.03	–	–
		MA	21	–	–	–	–	–	–	–
		MO	46	–	0.14 (0.02–1.17)	0.07	0.14 (0.02–1.17)	0.07	–	–

*Two study populations from Colson et al. (2004) (6).
†Two study populations from Colson et al. (2005) (12).
HWE, *P*-value from exact test for the Hardy–Weinberg Equilibrium; MA, migraine with aura; MO, migraine without aura; *ESR-1*, oestrogen receptor 1 gene; *PGR*, progesterone receptor gene.

suggested that there may be a moderately increased association for having any migraine among Caucasians, which appeared strongest in a dominant model (pooled OR 1.49; 95% CI 0.98–2.26). While the direction and association of the effect estimates among Caucasians were similar for both migraine subgroups, they only reached statistical significance in MA (dominant mode: pooled OR 1.49; 95% CI 1.10–2.01), but not MO (dominant mode: pooled OR 1.56; 95% CI 0.79–3.09). Heterogeneity across all studies was medium to high for any migraine, MA, and MO; it was low among the studies investigating MA among Caucasians (dominant mode: $I^2 = 4.3\%$). This may support the significant results for Caucasians among MA.

Sensitivity analyses

For some of our analyses, Galbraith plots identified individual studies as important sources of heterogeneity. We performed sensitivity analyses by excluding studies that fell outside the margin set by the z score ± 2 SD.

For the association between the *ESR-1* 594 G > A polymorphism and migraine Galbraith plots did not identify individual studies as significant sources of heterogeneity for any migraine and MO (dominant model). One study (6) was excluded when looking at MA, which lowered the effect estimates; however, the association remained statistically significant (dominant mode: pooled OR 1.18; 95% CI 1.01–1.38).

For the association between *ESR-1* 325 C > G polymorphism and any migraine, MA, and MO, Galbraith plots did not identify individual studies as important sources of heterogeneity in any of the models.

For the association between the *ESR-1* Pvu II C > T polymorphism and migraine, we did not perform a formal sensitivity analysis, because: (i) only two studies were pooled; and (ii) the heterogeneity index was high, suggesting that pooled results need to interpreted with caution.

Effect estimates from the sensitivity analysis did not change the association between the *PGR* PROGINS insert polymorphism and migraine. They were all slightly higher for any migraine, MA, and MO assuming additive or dominant models. For example, after excluding two studies (8,12), the pooled OR for the association with any migraine assuming a dominant model was 1.34 (95% CI 0.74–2.41).

Discussion

The results of this meta-analysis suggest an association between the *ESR-1* 594 G > A and 325 C > G polymorphisms and migraine. The risk for MA and MO appears to increase by 40–60% for each of the variants and follows a dominant model in case of the *ESR-1*

Table 4. Association between sex hormone receptor polymorphisms and migraine, heterogeneity, and publication bias

Genetic model	Population	Studies, *n*	Relative risk (95% CI)	Heterogeneity				Publication bias	
				Q	df	*P*-value	I^2 (in %)	*P*-value Begg	*P*-value Egger
			ESR-1 594 G > A (rs2228480)						
Any migraine									
Additive	All (6,7,10)	4*	1.37 (1.02–1.83)	10.6	3	0.01	71.6	0.50	0.44
	Women (6,10)	3*	1.40 (0.88–2.24)	12.2	2	0.002	83.6	0.60	0.48
	Men (6,10)	3*	1.59 (1.10–2.30)	1.8	2	0.41	0	0.60	0.85
Dominant	All (6,7,10)	4*	1.50 (1.10–2.06)	8.4	3	0.04	64.5	0.17	0.47
	Women (6,10)	3*	1.56 (0.98–2.48)	7.5	2	0.02	73.5	0.60	0.53
	Men (6,10)	3*	1.80 (1.16–2.80)	0.2	2	0.89	0	0.60	0.82
Recessive	All (6,7,10)	4*	1.34 (0.74–2.43)	6.6	3	0.08	54.8	0.17	0.33
	Women (6,10)	3*	1.38 (0.49–3.89)	10.4	2	0.006	80.7	0.12	0.11
	Men (6,10)	3*	1.62 (0.32–8.28)	4.7	2	0.10	57.2	0.12	0.46
Migraine with aura									
Additive	All (6,7,9,10)	5*	1.30 (0.99–1.70)	16.5	4	0.002	75.8	1	0.72
	Women (6,10)	3*	1.41 (0.86–2.32)	11.5	2	0.003	82.6	0.12	0.24
	Men (6,10)	3*	1.64 (1.09–2.48)	2.0	2	0.38	0	0.60	0.71
Dominant	All (6,7,9,10)	5*	1.39 (1.02–1.89)	13.9	4	0.01	71.3	1	0.61
	Women (6,10)	3*	1.55 (0.94–2.56)	7.3	2	0.03	72.7	0.60	0.26
	Men (6,10)	3*	1.82 (1.09–3.04)	0.7	2	0.70	0	0.60	0.43
Recessive	All (6,7,9,10)	5*	1.35 (0.76–2.38)	10.3	4	0.04	61.2	1	0.77
	Women (6,10)	3*	1.49 (0.50–4.42)	9.5	2	0.01	78.9	0.12	0.03
	Men (6,10)	3*	2.02 (0.32–12.75)	5.3	2	0.07	62.5	0.12	0.09
Migraine without aura									
Additive	All (6,7,10)	4*	1.25 (1.01–1.55)	3.1	3	0.38	3.2	0.50	0.75
	Women (6,10)	3*	1.26 (0.81–1.95)	5.1	2	0.08	60.6	0.60	0.57
	Men (6,10)	3*	1.50 (0.88–2.57)	2.1	2	0.36	3.4	0.12	0.28
Dominant	All (6,7,10)	4*	1.41 (1.03–1.92)	4.3	3	0.24	29.5	0.17	0.83
	Women (6,10)	3*	1.42 (0.79–2.54)	5.5	2	0.06	63.5	0.60	0.64
	Men (6,10)	3*	1.71 (0.94–3.12)	1.3	2	0.52	0	0.12	0.23
Recessive	All (6,7,10)	4*	1.00 (0.57–1.74)	0.4	3	0.94	0	0.17	0.23
	Women (6,10)	3*	1.00 (0.49–2.05)	2.4	2	0.3	16.5	0.12	0.24
	Men (10)	1	2.38 (0.32–17.52)	–	–	–	–	–	–
*Two studies from Colson et al. (2004) (6).									
			ESR-1 325 C > G (rs1801132)						
Any migraine									
Additive	All (5,7,8,10,11)	5	1.16 (1.03–1.32)	1.6	4	0.81	0	0.05	0.04
	Caucasians (5,7,10,11)	4	1.19 (1.03–1.36)	1.3	3	0.73	0	0.04	0.06
	Women (5,8,10,11)	4	1.30 (1.09–1.55)	3.5	3	0.32	14.3	0.17	0.43
	Men (5,8,10,11)	4	0.91 (0.70–1.19)	2.6	3	0.45	0	0.17	0.70
Dominant	All (5,7,8,10,11)	5	1.16 (0.99–1.37)	1.9	4	0.75	0	0.14	0.30
	Caucasians (5,7,10,11)	4	1.17 (0.98–1.40)	1.9	3	0.59	0	0.50	0.40
	Women (5,8,10,11)	4	1.33 (1.08–1.64)	2.5	3	0.47	0	0.17	0.33
	Men (5,8,10,11)	4	0.96 (0.64–1.44)	4.3	3	0.23	30.7	0.50	0.20
Recessive	All (5,7,8,10,11)	5	1.40 (0.93–2.11)	6.5	4	0.16	38.9	1	0.80
	Caucasians (5,7,10,11)	4	1.54 (0.94–2.54)	5.0	3	0.17	40.4	0.50	0.39
	Women (5,8,10,11)	4	1.68 (0.95–2.96)	5.7	3	0.13	47.5	0.50	1.00
	Men (5,8,10,11)	4	0.72 (0.37–1.41)	2.0	3	0.57	0	0.50	0.39

(continued)

Table 4. Continued

Genetic model	Population	Studies, *n*	Relative risk (95% CI)	Heterogeneity Q	df	*P*-value	I^2 (in %)	Publication bias *P*-value Begg	*P*-value Egger
Migraine with aura									
Additive	All (5,7–11)	6	1.18 (1.06–1.32)	1.8	5	0.88	0	0.57	0.95
	Caucasians (5,7,9–11)	5	1.20 (1.07–1.34)	0.8	4	0.94	0	1	0.35
	Women (8,10,11)	3	1.29 (0.91–1.82)	4.9	2	0.09	58.8	0.12	0.24
	Men (8,10,11)	3	0.89 (0.59–1.34)	2.3	2	0.32	13.0	0.12	0.01
Dominant	All (5,7–11)	6	1.15 (1.00–1.31)	2.8	5	0.74	0	0.85	0.62
	Caucasians (5,7,9–11)	5	1.16 (1.01–1.34)	2.3	4	0.68	0	0.62	0.35
	Women (8,10,11)	3	1.28 (0.86–1.90)	3.8	2	0.15	47.4	0.12	0.25
	Men (8,10,11)	3	0.84 (0.48–1.50)	2.6	2	0.27	24.0	0.60	0.15
Recessive	All (5,7–11)	6	1.60 (1.19–2.17)	5.6	5	0.35	10.6	0.35	0.43
	Caucasians (5,7,9–11)	5	1.75 (1.30–2.34)	3.8	4	0.43	0	1	0.58
	Women (8,10,11)	3	1.93 (0.95–3.92)	3.7	2	0.16	46.1	0.60	0.85
	Men (8,10,11)	3	0.92 (0.37–2.28)	0.8	2	0.68	0	0.60	0.88
Migraine without aura									
Additive	All (5,7,8,10,11)	5	1.12 (0.96–1.31)	2.4	4	0.67	0	0.05	0.02
	Caucasians (5,7,10,11)	4	1.11 (0.93–1.33)	2.3	3	0.50	0	0.17	0.06
	Women (8,10,11)	3	1.33 (1.07–1.66)	1.0	2	0.60	0	0.60	0.54
	Men (8,10,11)	3	0.95 (0.66–1.36)	1.3	2	0.52	0	0.60	0.42
Dominant	All (5,7,8,10,11)	5	1.09 (0.89–1.34)	2.3	4	0.67	0	0.33	0.30
	Caucasians (5,7,10,11)	4	1.05 (0.84–1.32)	1.9	3	0.59	0	0.17	0.33
	Women (8,10,11)	3	1.29 (0.96–1.72)	0.5	2	0.78	0	0.60	0.53
	Men (8,10,11)	3	0.98 (0.59–1.64)	2.4	2	0.29	18.3	0.60	0.81
Recessive	All (5,7,8,10,11)	5	1.44 (0.97–2.13)	4.3	4	0.37	6.5	0.62	0.51
	Caucasians (5,7,10,11)	4	1.65 (1.02–2.66)	3.2	3	0.37	4.9	0.17	0.14
	Women (8,10,11)	3	2.01 (1.19–3.41)	2.2	2	0.33	9.5	0.12	0.20
	Men (8,10,11)	3	0.77 (0.33–1.82)	0.6	2	0.75	0	0.60	0.68
			ESR-1 Pvu II C > T (rs2234693)						
Any migraine									
Additive	All (5,8)	2	1.31 (0.58–2.96)	15.3	1	<0.0001	93.5	0.32	–
	Women (5,8)	2	1.40 (0.67–2.93)	8.5	1	0.004	88.2	0.32	–
	Men (5,8)	2	1.13 (0.43–3.00)	7.1	1	0.01	85.8	0.32	–
Dominant	All (5,8)	2	1.53 (0.60–3.92)	9.4	1	0.002	89.4	0.32	–
	Women (5,8)	2	1.60 (0.76–3.39)	4.2	1	0.04	76.3	0.32	–
	Men (5,8)	2	1.38 (0.34–5.65)	6.1	1	0.01	83.6	0.32	–
Recessive	All (5,8)	2	1.20 (0.44–3.28)	7.3	1	0.01	86.3	0.32	–
	Women (5,8)	2	1.41 (0.49–4.10)	5.2	1	0.02	80.7	0.32	–
	Men (5,8)	2	0.86 (0.34–2.15)	2.2	1	0.14	54.6	0.32	–
Migraine with aura									
Additive	All (5,8)	2	1.41 (0.59–3.39)	11.0	1	0.001	90.9	0.32	–
	Women (8)	1	2.47 (1.45–4.19)	–	–	–	–	–	–
	Men (8)	1	1.90 (0.90–4.03)	–	–	–	–	–	–
Dominant	All (5,8)	2	1.97 (0.70–5.59)	6.4	1	0.01	84.4	0.32	–
	Women (8)	1	3.63 (1.72–7.69)	–	–	–	–	–	–
	Men (8)	1	2.87 (0.87–9.46)	–	–	–	–	–	–
Recessive	All (5,8)	2	1.07 (0.41–2.81)	4.4	1	0.04	77.3	0.32	–
	Women (8)	1	2.04 (0.76–5.43)	–	–	–	–	–	–
	Men (8)	1	1.74 (0.47–6.47)	–	–	–	–	–	–

(continued)

Table 4. Continued

Genetic model	Population	Studies, *n*	Relative risk (95% CI)	Heterogeneity Q	df	*P*-value	I^2 (in %)	Publication bias *P*-value Begg	*P*-value Egger
Migraine without aura									
Additive	All (5,8)	2	1.21 (0.54–2.72)	10.1	1	0.001	90.1	0.32	–
	Women (8)	1	1.82 (1.19–2.80)	–	–	–	–	–	–
	Men (8)	1	1.80 (0.99–3.29)	–	–	–	–	–	–
Dominant	All (5,8)	2	1.21 (0.41–3.57)	8.0	1	0.01	87.5	0.32	–
	Women (8)	1	1.80 (1.02–3.19)	–	–	–	–	–	–
	Men (8)	1	2.78 (1.16–6.67)	–	–	–	–	–	–
Recessive	All (5,8)	2	1.31 (0.48–3.54)	4.9	1	0.03	79.4	0.32	–
	Women (8)	1	2.92 (1.25–6.82)	–	–	–	–	–	–
	Men (8)	1	1.32 (0.44–3.95)	–	–	–	–	–	–
			PGR PROGINS insert						
Any migraine									
Additive	All (7,8,12)	4*	1.02 (0.55–1.87)	23.9	3	< 0.0001	87.5	0.50	0.37
	Caucasians (7,12)	3*	1.39 (0.94–2.06)	6.0	2	0.05	66.5	0.60	0.27
	Women (8,12)	3*	1.15 (0.44–2.97)	16.8	2	<0.0001	88.1	0.60	0.67
	Men (8,12)	3*	0.97 (0.28–3.39)	8.1	2	0.02	75.4	0.60	0.56
Dominant	All (7,8,12)	4*	1.06 (0.53–2.09)	24.5	3	< 0.0001	87.8	0.50	0.35
	Caucasians (7,12)	3*	1.49 (0.98–2.26)	5.3	2	0.07	62.5	0.60	0.18
	Women (8,12)	3*	1.26 (0.42–3.76)	19.2	2	<0.0001	89.6	0.60	0.83
	Men (8,12)	3*	0.91 (0.24–3.40)	7.4	2	0.03	72.9	0.60	0.58
Recessive	All (7,12)	3*	1.22 (0.59–2.55)	2.0	2	0.37	0.7	0.60	0.56
	Caucasians (7,12)	3*	1.22 (0.59–2.55)	2.0	2	0.37	0.7	0.60	0.56
	Women (12)	2*	1.11 (0.34–3.69)	0.1	1	0.81	0	0.32	–
	Men (12)	1	1.97 (0.17–22.26)	–	–	–	–	–	–
Migraine with aura									
Additive	All (7,8,12)	4*	1.11 (0.68–1.81)	10.9	3	0.01	72.6	0.17	0.08
	Caucasians (7,12)	3*	1.40 (1.05–1.86)	2.5	2	0.29	18.8	0.60	0.59
	Women (8)	1	0.44 (0.19–1.06)	–	–	–	–	–	–
	Men	0	–	–	–	–	–	–	–
Dominant	All (7,8,12)	4*	1.13 (0.65–1.96)	11.1	3	0.01	72.9	0.17	0.04
	Caucasians (7,12)	3*	1.49 (1.10–2.01)	2.1	2	0.35	4.3	0.60	0.42
	Women (8)	1	0.44 (0.19–1.06)	–	–	–	–	–	–
	Men (8)	0							
Recessive	All (7,12)	3*	1.59 (0.70–3.61)	1.0	2	0.59	0	0.60	0.58
	Caucasians (7,12)	3*	1.59 (0.70–3.61)	1.0	2	0.59	0	0.60	0.58
	Women	0	–	–	–	–	–	–	–
	Men	0	–	–	–	–	–	–	–
Migraine without aura									
Additive	All (7,8,12)	4*	1.01 (0.48–2.13)	20.0	3	<0.0001	85.0	0.50	0.70
	Caucasians (7,12)	3*	1.42 (0.79–2.57)	7.3	2	0.03	72.5	0.60	0.38
	Women (8)	1	0.36 (0.16–0.82)	–	–	–	–	–	–
	Men (8)	1	0.14 (0.02–1.17)	–	–	–	–	–	–
Dominant	All (7,8,12)	4*	1.06 (0.45–2.50)	21.5	3	< 0.0001	86.0	1	0.76
	Caucasians (7,12)	3*	1.56 (0.79–3.09)	7.5	2	0.02	73.5	0.60	0.65
	Women (8)	1	0.36 (0.16–0.82)	–	–	–	–	–	–
	Men (8)	1	0.14 (0.02–1.17)	–	–	–	–	–	–

(continued)

Table 4. Continued

Genetic model	Population	Studies, *n*	Relative risk (95% CI)	Heterogeneity				Publication bias	
				Q	df	*P*-value	I^2 (in %)	*P*-value Begg	*P*-value Egger
Recessive	All (7,12)	2	1.28 (0.19–8.76)	2.6	1	0.11	61.3	0.32	–
	Caucasians (7,12)	2	1.28 (0.19–8.76)	2.6	1	0.11	61.3	0.32	–
	Women	0	–	–	–	–	–	–	–
	Men	0	–	–	–	–	–	–	–

*Two studies from Colson et al. (2005) (12).

594 G > A and a recessive model in case of the *ESR-1* 325 C > G polymorphism. In contrast, pooled results for the *ESR-1* Pvu II C > T and the *PGR* PROGINS insert polymorphisms did not suggest an association with migraine. This pattern of association may differ by ethnicity. However, while most studies were conducted in Caucasian populations, only one was done in an Indian population (8), which does not allow an evaluation among non-Caucasian populations. Further, given a lack of replication studies, we cannot conclusively assess an association of additional polymorphisms in *ESR-1* (7,9), *AR* (12), *FSHR* (11), *ESR-2* (11), *CYP19A1* (11), and *NRIP1* (11) with migraine or migraine subgroups.

Evidence from population-based, clinical, and physiological studies suggests a pivotal role for sex hormones in the pathogenesis of migraine (2–4). In addition, association studies have investigated multiple variants in genes coding for sex hormone receptors or proteins involved in their pathways and metabolism. Among those, multiple studies looked at the *ESR-1* 594 G > A (6,7,9,10), *ESR-1* 325 C > G (5,7–11), *ESR-1* Pvu II C > T (5,8), *ESR-1* 30 T > C (7,9), and *PGR* PROGINS insert (7,8,12) polymorphisms. Apart from the two studies that did not find an association between the *ESR-1* 30 T > C polymorphism and migraine, results from studies in the other polymorphisms were contradictory.

ESR-1 is located on chromosome 6q25.1 and has eight exons (18). The receptor is expressed, for example, in the hypothalamus, limbic system, hippocampus, and the brainstem of the human brain (19), regions which are implicated in many pain syndromes including migraine. The *ESR-1* 594 G > A (exon 8) and 325 C > G (exon 4) polymorphisms are synonymous, hence, their functional implication is unknown (20). While our results support that the variant alleles are associated with an increased risk for migraine, they are likely not causative, since they do not alter the amino acid sequence of the receptor. They may be in linkage disequilibrium with another causative variant or set of variants (haplotype) within *ESR-1*. The Pvu II C > T polymorphism is intronic, thus located in a non-coding region. It does not alter the protein sequence, but may affect splicing and thus modify protein production (21). While our overall pooled results do not support a role for this variant in migraine, the individual results from the two available studies may suggest a difference between Caucasians (5) and Indians (8) (also reflected by the large heterogeneity for the pooled effect estimates). We may speculate that post-transcriptional modification such as splicing differs between ethnic groups. *PGR* is located on chromosome 11q22 (22). Progesterone receptors are located in various human brain regions (23) and their expression is regulated by oestrogen and progesterone levels (24). The PROGINS polymorphism is a 306-bp long *Alu* insertion in intron 7 and may negatively affect progesterone receptor expression (25). Our pooled analysis suggests that this *Alu* insert increases the risk for migraine only among Caucasians.

Study limitations

Some limitations need to be considered:

1. Migraine is biologically heterogeneous. Although, in all studies, patients were classified according to the criteria established by the International Headache Society (26,27), the clinical spectrum among patients is wide, which may be a source of misclassification.
2. While sample sizes for migraineurs and controls in the studies are about 200 or more (Table 1), power to detect overall and more so gender- or aura-specific associations in subgroups may not be adequate. In addition, not all studies looking at one polymorphism investigated any migraine and also presented stratified analyses according to aura subtype and gender. Further, the total number of studies identified was eight, which is limited. These studies looked at many different gene variants and not all studies investigated the same ones. For example, there were only two studies investigating the *ESR-1* Pvu II C > T polymorphism with conflicting results (5,8). The non-significant results from the pooled analysis may be due to insufficient pooled sample size.

3. Power also depends on the minor allele frequencies of the polymorphisms investigated. For example, the minor allele frequency for the *PGR* PROGINS insert polymorphism is less than 10% in some of the studies leaving few or no observations among the homozygous '22' carriers. Although pooling available study results increases precision and power, there may still be remaining uncertainties.
4. Initial publications of genetic association studies often report positive associations, while successive ones do not find an association. We have performed this meta-analysis at an early stage; however, we still consider it valuable. While the systematic review part allows an overview of the available studies including individual results, the meta-analytic part also enables evaluation of magnitude and direction of combined results from pooled effect estimates including sources of heterogeneity.
5. Ethnicity may be a source of heterogeneity in the association between polymorphisms in genes coding for proteins in sex hormone receptor pathways and metabolism and migraine. The available data suggest this for the *ESR-1* Pvu II C > T and *PGR* PROGINS insert polymorphisms. However, only one study was performed in a non-Caucasian population.
6. Residual heterogeneity among Caucasians for the *ESR-1* 594 G > A, *ESR-1* Pvu II C > T, and *PGR* PROGINS insert polymorphisms were medium to high, indicating that the effect estimates carry further unidentified sources of uncertainties. In addition, the results from the single study among Indians (8), suggesting an increased risk for migraine among carriers of the *ESR-1* Pvu II T allele and a reduced risk among carriers of the *PGR* PROGINS *Alu* insertion await replication.
7. In one study (10), genotype distribution of *ESR-1* 594 G > A and 325 C > G and in another (8) of *ESR-1* Pvu II C > T was in Hardy–Weinberg Disequilibrium.
8. We only used extractable data from the papers. One (9) of two (7,9) studies investigating the *ESR-1* 30 T > C polymorphism did not allow us to extract genotype frequencies; hence, we could not calculate pooled effect estimates. However, both studies did not find an association with migraine, which would likely not change in a pooled analysis.
9. Since we did not have primary data among the studies investigating multiple polymorphisms, we were not able to perform haplotype analyses or investigate potential gene–gene interactions. Such interactions were suggested by individual studies (8,11).

Conclusions and outlook

Additional research is warranted to delineate further the association between gene variants coding for proteins in sex hormone receptor pathways and metabolism and migraine, among Caucasian and more so among non-Caucasian populations. We suggest the following criteria to be applied in future studies:

1. Studies need to be adequately powered. Power in genetic association studies is determined by both sample size and allele frequencies. Sample sizes of at least several hundred migraineurs and non-migraineurs are needed to detect at least moderate associations. If the minor allele frequency of a polymorphism investigated is low, the sample size must be further increased to have adequate power.
2. Results should not just be presented overall, but also stratified by gender and migraine aura status. This must also be considered with regard to power.
3. Investigators should use standardized migraine classification including aura status.
4. Analyses should focus on main gene effects first, since power to detect gene–gene interactions is often limited.

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